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Methods for Transition Metal Catalyzed C-N Bond Formation and Organocatalytic Allylation of Aldehydes

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Center for Sustainable and Green Chemistry

Technical University of Denmark DTU

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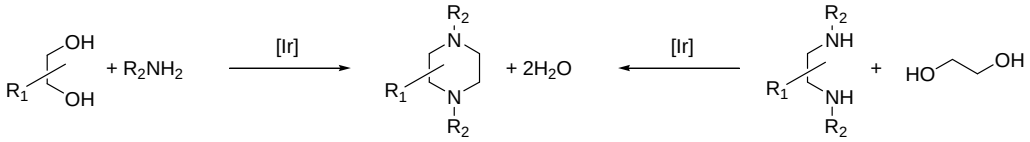
Lars Ulrik Rubæk Nordstrøm

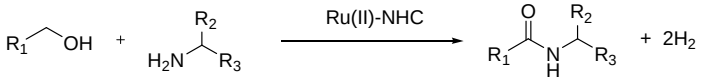
Abstract

The projects described in this thesis are centered on method development in catalysis. The projects carried out at DTU dealt with the catalytic formation of C-N bonds by iridium and ruthenium complexes. In the first project diols and (di)amines were coupled to form piperazines. The reaction was catalyzed by the commercially available $[Cp^*IrCl_2]_2$ complex and released water as the only by-product. The reaction conditions were optimized, and the substrate scope was explored. Considerable work was done to extend the reaction to facilitate the synthesis of other *N*-heterocycles, but this part was largely unsuccessful.



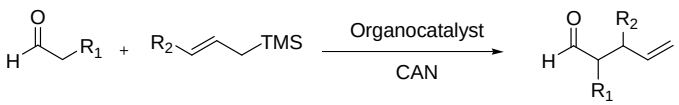
Scheme i: Ir catalyzed synthesis of piperazines from diols and (di)amines.

The next project was the development of a dehydrogenative coupling of alcohols and amines to produce amides. We found that Ru(II)-NHC complexes catalyzed this reaction efficiently. This reaction is notable because no stoichiometric oxidant is needed because hydrogen gas is released from the reaction mixture. The catalytic system was optimized, and the substrate scope was investigated.



Scheme ii: Synthesis of amides from alcohols and amines by extrusion of hydrogen gas.

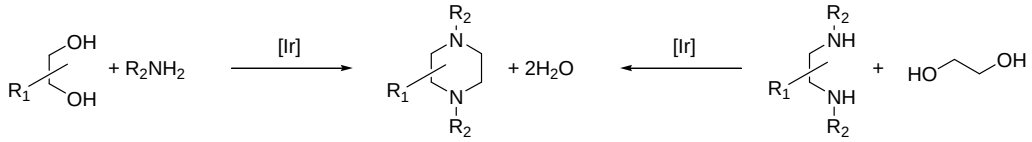
During the external stay in the MacMillan group an organocatalytic reaction between aldehydes and 1,2-disubstituted allylsilanes was investigated. The reaction creates two new stereocenters. Thorough optimization studies were performed, but unfortunately it was not possible to obtain useful yields, even though the d.r. was acceptable and the *ee* was good. Efforts to design a new catalyst gave a promising lead, but time limitations prevented further catalyst development.



Scheme iii: Organocatalytic SOMO reaction between aldehydes and 1,2-disubstituted allylsilanes.

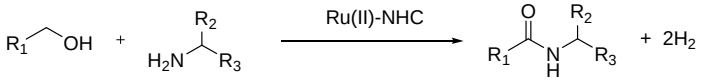
Resumé

Denne afhandling omhandler forskellige projekter, som alle fokuserer på metodeudvikling inden for katalyse. Projekterne som blev udført på DTU drejede sig som katalytisk dannelse af C-N bindinger vha. iridium og ruthenium komplekser. I det første projekt blev dioler og (di)aminer koblet og dannede piperaziner. Reaktionen katalyseres af det kommercielt tilgængelige $[Cp^*IrCl_2]_2$ kompleks og udskiller vand som det eneste biprodukt. Reaktionsbetingelserne blev optimeret og tolerancen i forhold til substraterne blev undersøgt. Derefter blev det forsøgt at udvide reaktionen til at muliggøre syntesen af andre *N*-heterocykler, men denne del af projektet var ikke succesfuldt.



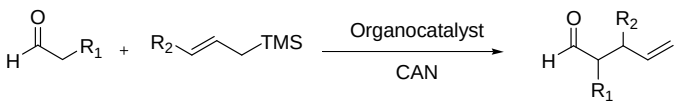
Skema i: Ir-katalyseret syntese af piperaziner ud fra dioler og (di)aminer.

Det næste projekt var udviklingen af en oxidativ kobling af alkoholer og aminer med amider som produkter. Vi fandt, at Ru(II)-NHC komplekser er effektive katalysatorer for denne reaktion. Reaktionen er bemærkelsesværdig, fordi den ikke kræver en støkiometrisk mængde oxidant eftersom hydrogengas frigives fra reaktionsblandingen. Katalysatorsystemet blev optimeret og substrattolerance blev undersøgt.



Skema ii: Syntese af amider ud fra alkoholer og aminer ved fraspaltning af hydrogengas.

Under udlandsopholdet i MacMillans gruppe blev en organokatalytisk reaktion mellem aldehyder og 1,2-disubstituerede allylsilaner undersøgt. Reaktionen danner to nye stereocentre. På trods af at et grundig optimeringsstudie blev udført var det desværre ikke muligt at opnå brugbare udbytter, selvom d.r. var acceptabelt og *ee* var godt. Forsøg på at udvikle en ny katalysator gav et lovende resultat, men tidsmangel forhindrede yderligere katalysatorudvikling.



Skema iii: Organokatalytisk SOMO-reaktion mellem aldehyder og 1,2-disubstituerede allylsilaner.

List of abbreviations

Ac	Acetyl	DCC	*N*,*N*'-Dicyclohexyl-carbodiimide
Adm	Adamantyl		
aq.	Aqueous	DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
Ar	Aromatic		
ax	Axial	DFT	Density functional theory
b	Broad (NMR)	DIBAL-H	Diisobutylaluminum hydride
BAr_F	Tetrakis[3,5-bis(trifluoromethyl) phenyl]borate	DMAP	4-(Dimethylamino)-pyridine
BINAP	2,2'-Bis(diphenyl phosphino)-1,1'-binaphthyl	DME	1,2-Dimethoxyethane
		DMF	*N*,*N*-Dimethylformamide
		DMSO	Dimethyl sulfoxide
Bn	Benzyl	DNBA	Dinitrobenzoic acid
Boc	*tert*-Butoxycarbonyl	dppb	1,4-Bis(diphenyl-phosphino)butane
bpy	2,2'-Bipyridine		
BTA	Bis(trifluoromethane sulfon)amide	dppe	1,2-Bis(diphenyl-phosphino)ethane
Bu	Butyl	dppf	1,1'-Bis(diphenyl-phosphino)ferrocene
c	Cyclo or concentration		
CAM	Cerium ammonium molybdate	dppp	1,3-Bis(diphenyl-phosphino)propane
CAN	Ceric ammonium nitrate	d.r.	Diastereomeric ratio
CBS	Corey-Bakshi-Shibata	DTBP	2,6-Di-*tert*-butyl pyridine
COD	1,5-Cyclooctadiene	*E*	Entgegen or electrophile
Cp*	Pentamethylcyclo-pentadienyl	*ee*	Enantiomeric excess
		ent	Enantiomeric
Cy	Cyclohexyl	eq	Equation or equatorial
Cyp	Cyclopentyl	equiv	Equivalents
d	Doublet (NMR)	Et	Ethyl
DCA	Dichloroacetic acid	GC	Gas chromatography

h	Hour(s)
HBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyl-uronium hexafluorophosphate
Hex	Hexyl
HOBt	1-Hydroxybenzotriazole
HMPA	Hexamethylphosphor-amide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
i	Iso
IMe	1,3-Dimethylimidazol-2-ylidene
IMes	1,3-Dimesitylimidazol-2-ylidene
IR	Infrared spectroscopy
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
M	Molar
MCR	Multi-component reaction
Me	Methyl
Mes	Mesityl
Mp	Melting point
MS	Mass spectrometry
MW	Micro waves
n	Normal
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
o	Ortho
Oct	Octyl
p	Para
Pent	Pentyl
Ph	Phenyl
phen	1,10-Phenanthroline
PHOX	Phosphinooxazoline
ppm	Parts per million
Pr	Propyl
Pyr	Pyridine
q	Quartet (NMR)
R_f	Retension factor
r.t.	Room temperature
s	Singlet (NMR)
SOMO	Singly occupied molecular orbital
SFC	Supercritical fluid chromatograohy
t	Triplet (NMR)
TADDOL	α,α,α',α'-Tetraaryl-1,3-dioxolan-4,5,dimethanol
TCA	Trichloroacetic acid

tert, *t*	Tertiary	TMS	Tetramethylsilane or Trimethylsilyl
TFA	Trifluoroacetic acid		
Tf	Trifluoromethane-sulfonyl	tol	Tolyl
		Ts	*p*-Toluenesulfonyl; Tosyl
THF	Tetrahydrofuran	TTP	*meso*-Tetrakis(*p*-tolyl) porphyrin
TLC	Thin layer chromatography		
		Z	Zusammen
TMEDA	*N*,*N*,*N*',*N*'-Tetramethyl-ethylenediamine		

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Appendix A

Nordstrøm, L. U.; Madsen, R. 'Iridium catalysed synthesis of piperazines from diols', *Chem. Commun.* **2007**, 5034-5036.

Appendix B

Nordstrøm, L. U.; Vogt, H.; Madsen, R. 'Amide synthesis from alcohols and amines by the extrusion of dihydrogen', *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.

1 Introduction: Sustainable Development and Catalysis

The synthesis of organic molecules is essential in modern society because of our reliance on products like polymers, pharmaceuticals, agricultural chemicals, food additives etc. For the synthesis of these products the chemical industry is heavily dependent on feed stocks derived from fossil sources. Crude oil and natural gas can be converted into bulk products, and these can then be converted into fine chemicals. It has been estimated that around 95 % of the carbon containing chemicals are ultimately derived from non-renewable resources.[1] The amount of fossil resources remaining is still a matter of debate, but it is obvious that the Earth's fossil resources will be depleted sooner or later. This will have a dramatic impact on our society and even before this happens prices will begin to rise drastically. To avoid some of these unfavorable changes it is important that the chemical industry switches from fossil to sustainable feed stocks. This can be achieved by developing methods to break biomass into simple petroleum-like compounds that can enter the existing pipelines. In the case of fine chemicals it could be advantageous to focus more on using the inherent complexity of natural products (*e.g.* carbohydrates) as building blocks.

Another critical challenge in the chemical industry is minimizing the amount of waste produced. While the petrochemical industry generates relatively low amounts of waste[a] the production of fine chemicals and especially pharmaceuticals generates enormous amounts of waste. To better help to quantify the amount of waste produced Roger Sheldon coined the term E factor (or *environmental impact factor*).[2] The E factor is defined in eq. 1.

$$\text{E factor} = \frac{\text{kg waste}}{\text{kg product}}$$

Equation 1: Definition of the E factor.

The E factor for the different classes of chemicals are usually in the ranges shown in table 1. The E factor is generally considered to be a good indication of the "greenness" of a certain process, but in each case it is important to judge the nature of the waste.

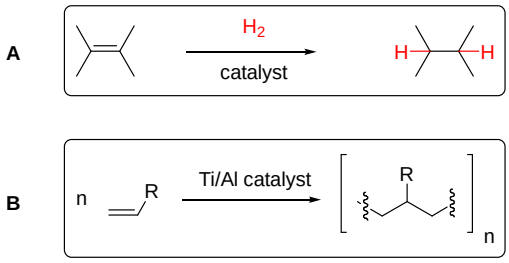
[a] Relative with respect to the amount of product produced, and not in absolute terms.

Chemical class	Product tonnage	E factor
Petrochemical	10^6 - 10^8	~ 0.1
Bulk	10^4 - 10^6	1 - 5
Fine	10^2 - 10^4	5 - 50
Pharmaceutical	10 - 10^3	25 - 100

Table 1: E factors for various types of chemicals (Numbers taken from ref. 2b).

Traditionally chemical synthesis has relied on stoichiometric reagents such as oxidants, reducing agents, coupling reagents etc. Since only a small part of these reagents is normally incorporated into the final product the reaction proceeds with poor atom economy[3] and consequently generates much waste.

To overcome the poor atom economy of many stoichiometric reagents, catalysts can be employed to facilitate more favorable reactions, and indeed catalysis has received an ever increasing attention in both academic and industrial settings over the last couple of decades.[4] Examples of processes with very good atom economy are hydrogenations of double or triple bonds[2b] (scheme 1A) and the Ziegler-Natta polymerization (scheme 1B).[5]



Scheme 1: A: Hydrogenation of a double bond.
B: Ziegler-Natta polymerization.

Both reducing the amounts of chemical waste produced and switching to sustainable feed stocks are essential if we want to avoid facing drastic environmental and economical changes in our society. This is in agreement with the conclusions reached by the Brundtland Commission (World Commission on Environment and Development): "*Humanity has the ability to make development sustainable to ensure that it meets the needs of the present without compromising the ability of future generations to meet their own needs*".[6]

The Center for Sustainable and Green Chemistry has undertaken several projects which all focus on developing new catalytic methods to utilize abundant bioresources in the

production of fuels, base- and fine-chemicals. This thesis will describe work done in the area of method development in homogeneous catalysis. The focus will primarily be on utilizing iridium and ruthenium catalysts for the formation of carbon-nitrogen bonds from alcohol and amine substrates. The targets are functionalities or scaffolds that are abundant in fine chemicals and therefore industrially relevant.

2 Method Development in Iridium Catalyzed Synthesis of *N*-Heterocycles

2.1 *N*-Heterocycles in Commercial Products

Cyclic nitrogen containing structures are important components in many organic compounds, and especially biologically active compounds such as pharmaceuticals,[7] agrochemical agents[8] and natural products[9] often contain *N*-heterocycles. A recent survey showed that 10 of the top 20 selling drugs contain *N*-heterocycles (US-market; 2006 figures).[10] As mentioned previously, the production of pharmaceuticals is the area that generally suffers most from large E factors, and consequently the development of new catalytic methods in this area is of great importance. A recent survey of the most common reactions in the industrial synthesis of drug candidates showed that heteroatom alkylation or acylation constituted 19 % of the total processes, making it the largest group of transformations.[11] *N*-Substitution accounted for 57 % of these, clearly showing that this type of reaction is an important area for the development of new and environmentally friendly synthesis methods.

2.1.1 Importance of piperazine and literature examples of syntheses

One of the so called privileged scaffolds in medicinal chemistry is the piperazine unit (**1**), which is found in many important drugs on the market (examples shown in figure 1). A study of 1000 orally administered drugs showed that 7 % of these contain the piperazine scaffold.[7a]

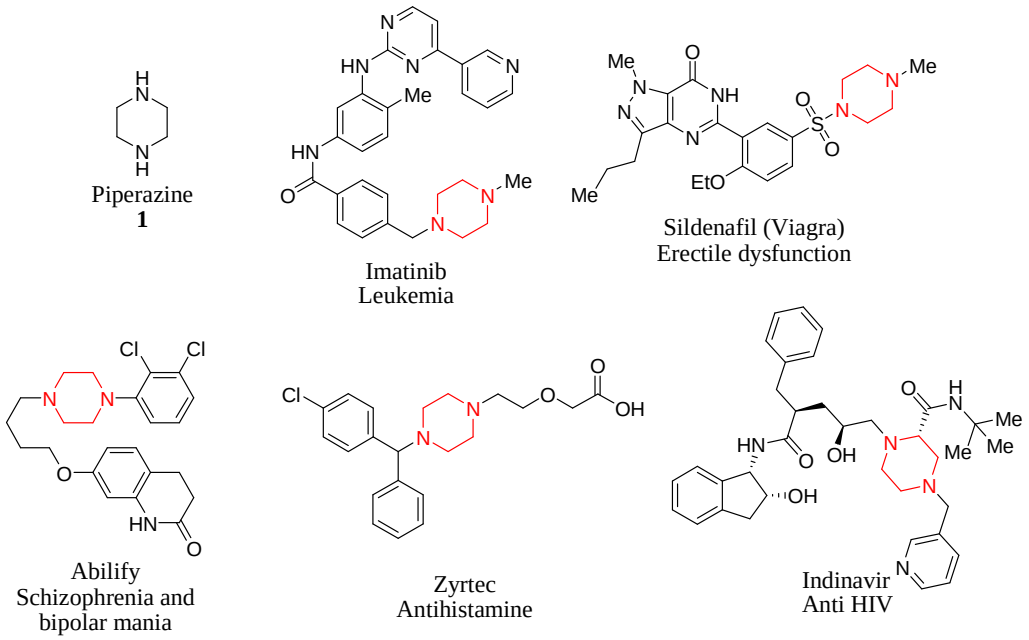
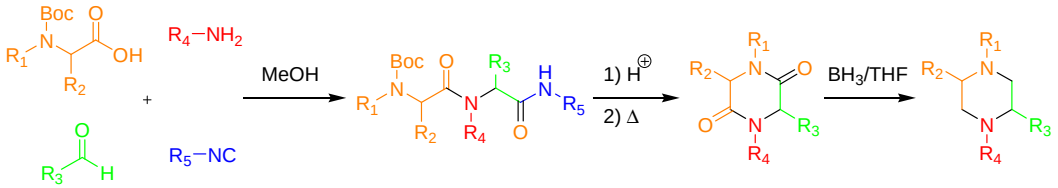


Figure 1: Structure of piperazine (1) and pharmaceuticals containing the piperazine subunit (in red).

Piperazine derivatives can be synthesized by numerous strategies. The most direct route is by substitution of an appropriate leaving group by the nitrogen atoms in piperazine.[12] The major drawback of this method is the demand for a good leaving group. If the reactants are supplied from sustainable sources alkyl halides are scarce, and therefore the abundant hydroxyl group must often serve this purpose. That means that the hydroxyl group must be activated or turned into a more reactive leaving group which inevitably results in stoichiometric amounts of waste. Furthermore, if the desired product is an unsymmetrically substituted piperazine over-alkylation toward the undesired symmetric product can be a problem.

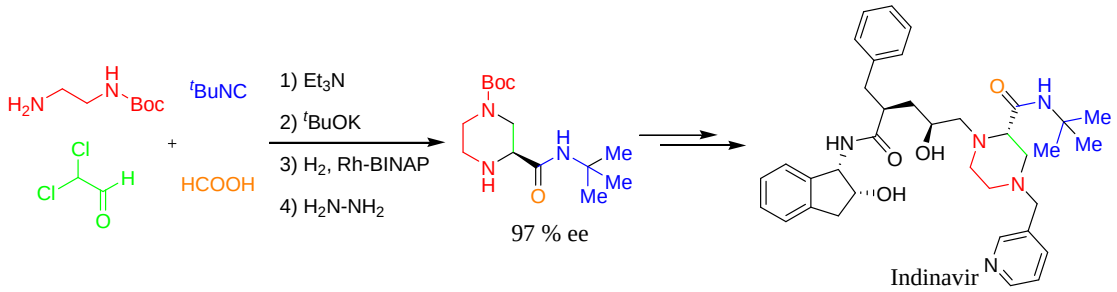
Reductive alkylation is another route to introduce *N*-substituents on piperazines,[13] but the process generates considerable amounts of waste from the reducing agent. The same disadvantages apply to the acylation/reduction method.[14]

When *C*-substituted piperazines are needed it is often necessary to construct the piperazine ring from simpler components. Multi-component reactions (MCR), especially the Ugi reaction,[15] have been very successful in this regard. Hulme's UDC (Ugi/de-Boc/cyclize) sequence leads to unsymmetrically substituted diketopiperazines[16] which can be reduced to the corresponding piperazines (scheme 2).[17]



Scheme 2: Synthesis of piperazines by MCR.

In Merck's improved synthesis of the important HIV protease inhibitor Indinavir (Crixivan™) an Ugi MCR is used to construct the central piperazine unit (scheme 3).[18]

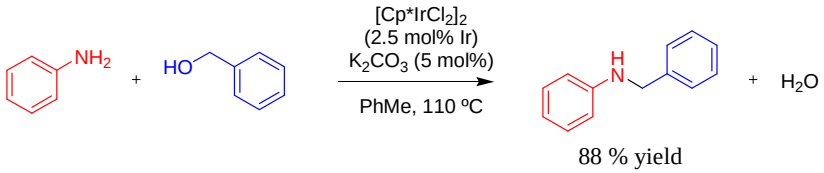


Scheme 3: Merck's use of the MCR in the synthesis of Indinavir.

While these MCRs are very elegant and generally effective at generating complexity, they also suffer from poor atom economy, and they often have to be carried out in multiple discrete steps.

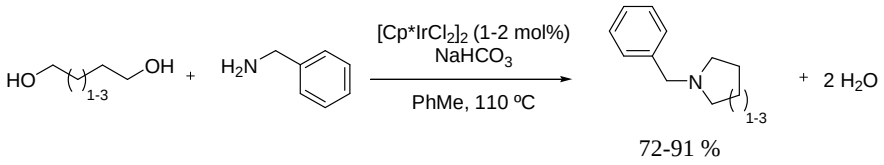
2.2 Iridium catalyzed *N*-alkylation with alcohols

Several methods for the alkylation of amines with alcohols have been reported using ruthenium[19] and iridium[20] catalysts (example shown in scheme 4).



Scheme 4: Example of *N*-alkylation with an alcohol (taken from ref. 20b).

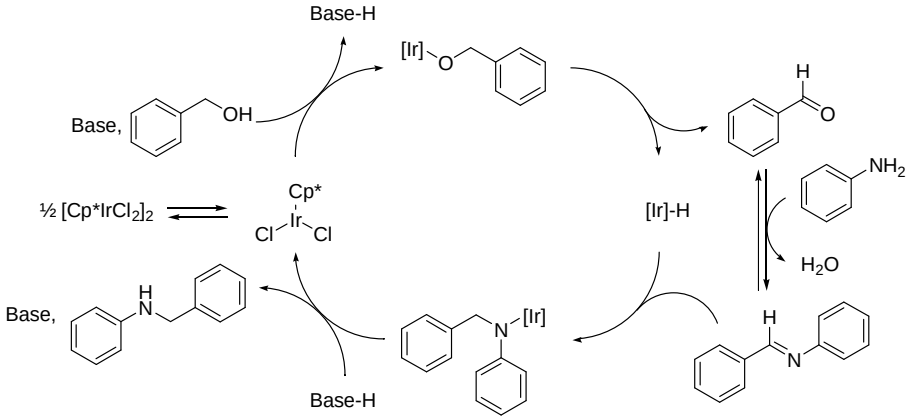
Using the same catalyst system as in scheme 4, Yamaguchi and co-workers have succeeded in cyclizing diols with primary amines to generate 5-, 6- and 7-membered cyclic amines (scheme 5).[21] The reaction is compatible anilines, benzyl- and alkyl-amines. The described scope of the diol partner is limited to benzyl alcohols and simple primary and secondary alkyl alcohols.



Scheme 5: Iridium catalyzed *N*-heterocyclization.

2.2.1 Mechanism

The dimeric 18-electron iridium complex $[Cp^*IrCl_2]_2$ is the most commonly used pre-catalyst for the *N*-alkylation with alcohols.[22] The mechanism is generally believed to proceed as illustrated in scheme 6.

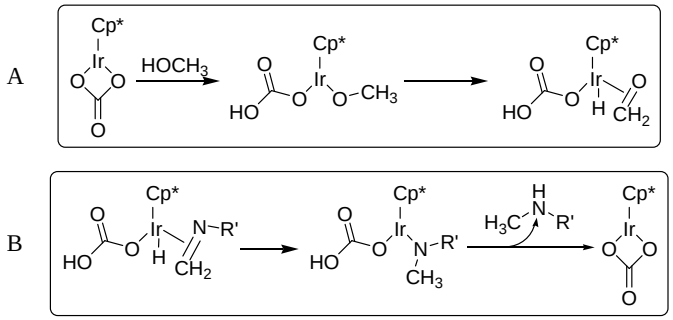


Scheme 6: Proposed mechanism for the *N*-alkylation of aniline with benzyl alcohol.

Initially, the active catalyst is formed by dissociation of the dimer into the monomer units. The alcohol then coordinates to the metal, and is deprotonated by the base to form an alkoxide complex. β-Hydride elimination generates an iridium-hydride species and an aldehyde. The aldehyde is released into the solution and condenses with the amine to form the corresponding imine. The imine is reduced to the amine by the iridium-hydride, and the active catalyst is reformed.

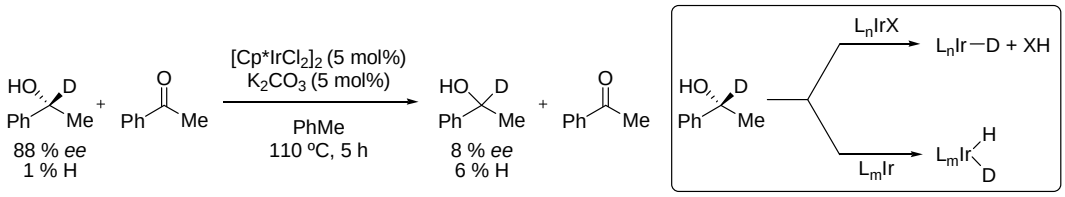
The mechanism has been studied in detail by several groups. Crabtree and co-workers used DFT calculations to find the lowest energy pathway.[23] They found that a bidentate carbonate as a ligand can lower the energy barriers in many of the high-energy steps. This is mainly due to its ability to assist in the protonation/deprotonation of the coordinated substrates. This is possible by switching between κ^1 and κ^2 coordination modes (scheme 7). Additionally, they found that dissociation of the product from the catalyst

could be the rate-determining step because the amines are stronger ligands than the other Lewis bases present in the reaction mixture.



Scheme 7: Crabtree's proposed mechanism for oxidation of the alcohol (A) and reduction of the imine (B). The mechanisms have been simplified by excluding certain high-energy intermediates.

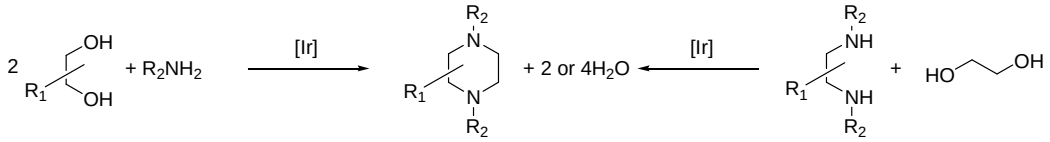
Yamaguchi and co-workers proposed that both amine and alkoxide coordinate to the metal center and that all steps, including imine formation, occur within the coordination sphere of the metal center.[24] This is in agreement with results from the Madsen group.[25] In a combined experimental and theoretical study it was found that (1) the substrates remain bound to the metal for the duration of the catalytic cycle, and (2) the amine present in large amounts compared to chloride and carbonate dominates as the ligand. Both of these finding are in contrast to Crabtree's results. Finally, adopting a racemization method described by Pàmies and Bäckvall[26] Madsen and co-workers demonstrated that the reaction goes through a mono-hydride intermediate, and not a di-hydride species (scheme 8) which could not have been ruled out previously. In the racemization experiment deuterated (*R*)-1-phenylethanol in 88 % *ee* was treated with the catalyst until the *ee* was 8 %. Since the deuterium in the racemized product remained at the carbon center the active catalyst must be a mono-hydride species. If the mechanism includes a di-hydride intermediate a much higher level of hydrogen-incorporation should have been observed.



Scheme 8: A racemization experiment (left) showed that a Ir-dihydride intermediate is not formed (see box).

2.3 Aim of the Project

Considering the importance of the piperazine unit in medicinal chemistry and the lack of environmentally friendly methods for its synthesis, we considered piperazines to be an excellent target for the development of a new catalytic methodology. In line with our desire to use substrates that could be derived from sustainable sources we decided to use alcohols and activate these by a suitable catalyst. The required nitrogen atoms could be supplied by mono-amines or 1,2-diamines. This strategy would make it possible to introduce different substituent patterns (scheme 9). Furthermore, the only byproduct from the reaction would be water, thus rendering the method very environmentally friendly. We also envisioned expanding the scope of the reaction to include the preparation of other *N*-heterocycles, such as pyrazines, iminosugars, pyrazoles, and pyrazolidines.

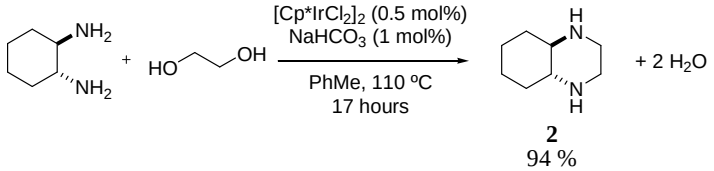


Scheme 9: Iridium catalyzed synthesis of substituted piperazines.

2.4 Results and Discussion

2.4.1 Synthesis of piperazines

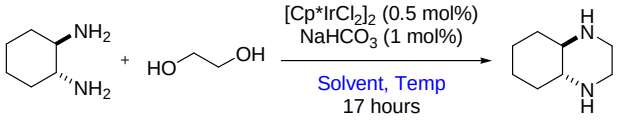
The initial test reaction was performed with a simple substrate combination: equimolar amounts of ethylene glycol and (±)-*trans*-1,2-diaminocyclohexane (scheme 10). Since the desired reaction is closely related to the *N*-heterocyclization described by Yamaguchi and co-workers[21] the same catalyst and reaction conditions were chosen for the test reaction. The reaction was performed in a sealed heavy-walled flask to ensure that no hydrogen was liberated from the reaction mixture.



2
94 %

Scheme 10: Synthesis of 2 from a 1,2-diamine and a 1,2-diol.

The reaction was carried out at 110 °C for 17 hours and resulted in a 94 % isolated yield of the bicyclic piperazine (**2**). In a second experiment the reaction was performed again and stopped after 5 hours, but the yield then dropped to 32 %. The next step was to examine the influence of the solvent. A wide range of solvents were tested and the results are summarized in table 2. To avoid build-up of high pressure the reactions were performed at the atmospheric boiling point of the solvent.



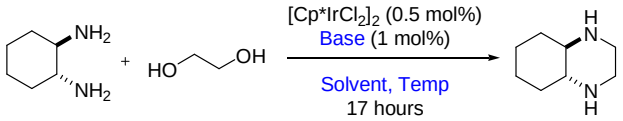
2

Entry	Solvent	Temperature (ºC)	Isolated yield (%)
1	Toluene	110	94
2	Heptane	98	13
3	THF	67	5
4	Dioxane	100	86
5	Water	100	96
6	Toluene	90	64

Table 2: Optimization of the piperazine synthesis with respect to the solvent.

Toluene gave the best result of the organic solvents (entry 1). This was expected because toluene is the solvent of choice in related reactions.[21] Heptane and THF performed very poorly and gave 13 and 5 % yield, respectively (entries 2 and 3). In the case of THF this might in part be due to the lower temperature. Dioxane gave a slightly lower yield than toluene (86 %, entry 4). Even though dioxane is not a preferred solvent in the medicinal industry due to environmental concerns[27] it might still be useful in cases where the substrates are insoluble in toluene. We speculated that since the catalyst tolerates the water released during the course of the reaction, water could also be used as the bulk solvent. To our delight, we obtained a yield of 96 % from this reaction. It is interesting to note that the large excess of water does not seem to hydrolyze the imine intermediate before it undergoes reduction. Also, we had been worried that excess of water might displace the alcohol and the imine as ligands on the metal center, but these concerns were unjustified. In a last experiment, the reaction was repeated in toluene at 90 °C, but this led to incomplete conversion after 17 hours.

We decided to continue with both water and toluene since the yields were essentially the same and still the solvation properties are very different. Water, being a very environmentally friendly (and cheap) solvent,[28] would be the first choice, but toluene can be useful for reactions with unpolar substrates.

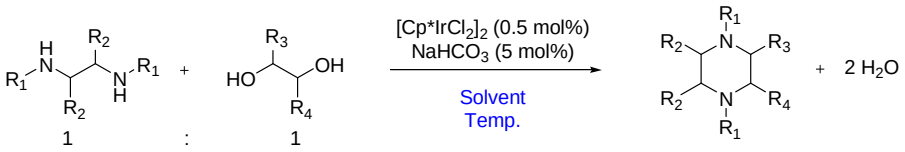


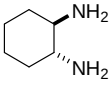
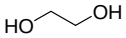
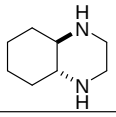
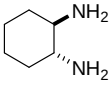
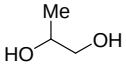
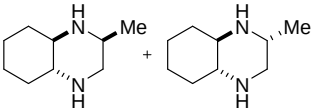
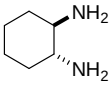
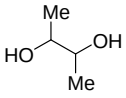
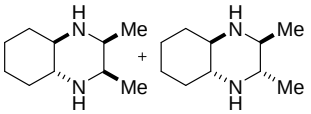
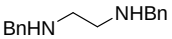
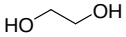
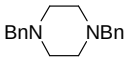
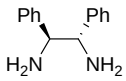
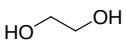
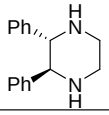
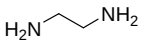
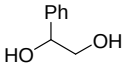
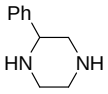
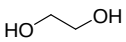
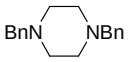
2

Entry	Solvent	Temperature (ºC)	Base	Isolated yield (%)
1	PhMe	110	$NaHCO_3$	94
2			None	78
3			Et_3N	94
4			NaOAc	53
5			Na_2CO_3	63
6	Water	100	$NaHCO_3$	96
7			None	41
8			NaOAc	48
9			Na_2CO_3	24

Table 3: Base screening in the synthesis of piperazine 2.

Analogous to the solvent's influence on the reaction, the base is known to play an important role, and therefore a range of bases were screened (table 3). In both toluene and water the absence of the base (entry 2 and 7, respectively) lead to a decrease in yield of **2**. This effect was more pronounced in water than in toluene. Substituting $NaHCO_3$ with NaOAc led in both solvents to a drastic decrease in yield. Also, a stronger base (Na_2CO_3) was tried but again, the result was a lower yield compared to $NaHCO_3$. Finally, Et_3N was used in toluene (entry 3) to probe if the solubility of the base had an impact on the yield. The result was identical to the experiment with $NaHCO_3$. Consequently, we decided to continue using $NaHCO_3$ in further experiments because it is easier to separate from the product.



Entry	(Di)amine	Diol	Solvent	Temp. (ºC)	Product(s)	Isolated yield (%) (d.r.)[a]
1			Water	100		96
			PhMe	110		94
2			Water	100		98 (>20:1)
			PhMe	110		87 (3:1)
3			Water	140		81 (3:1)
			PhMe	140		79 (1:1)
4			Water	140		73
			PhMe	140		74
5			Water	100		60[b]/86[c]
			PhMe	110		54[b]
6			Water	120		quant.
7	$BnNH_2$		Neat	160[d]		94

a: Determined from ^{1}H NMR. *b*: Reaction time 64 h. *c*: 10 mol% TFA was used instead of $NaHCO_3$. *d*: Reaction time 6 h.

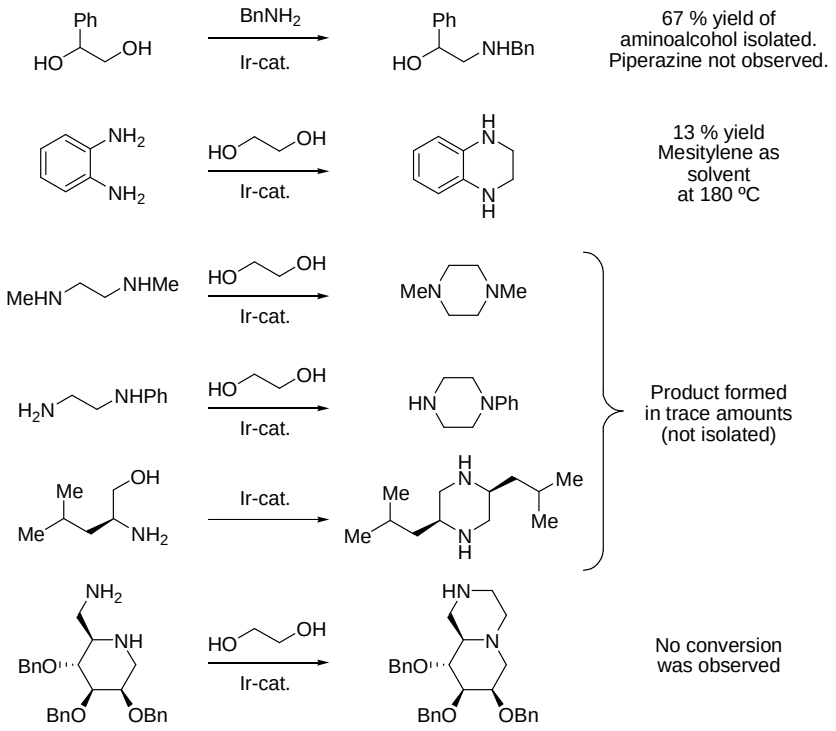
Table 4: Substrate scope of the Ir-catalyzed piperazine synthesis.

At this stage we moved on to explore the substrate scope of the reaction (table 4). When only one of the alcohol functionalities was a secondary alcohol (entry 2) the reaction proceeded smoothly to give the corresponding piperazine in high yields. In water the diastereoselectivity was excellent (>20:1) but it was only moderate (3:1) in toluene. With two secondary alcohols groups (entry 3) the reaction rate decreased significantly, and a higher temperature was needed to achieve full conversion. The selectivity was drastically reduced compared to the previous example, which might be due to the higher temperature. Secondary amines participated in the reaction too, albeit only at higher temperature (entry 4). It is interesting to note that this reaction works in water at elevated temperatures, although the iminium/enamine intermediate could be rapidly hydrolyzed

under these conditions. Next, we used a chiral diamine to examine whether the reaction conditions would erode the optical purity (entry 5). The optical rotation of the product was found to be identical to literature values, and thus we could conclude that no racemization had occurred. The reaction rates were, however, lower than in the other cases, and 64 hours were required to obtain an acceptable yield. With water as solvent we found that using a catalytic amount of TFA instead of $NaHCO_3$ greatly accelerated this reaction. After obtaining this result we went back to the earlier substrates, but TFA did not lead to improved yields or reaction rates in other cases. The simple 1,2-diaminoethane reacted smoothly with racemic 1-phenylethane-1,2-diol to give the piperazine in quantitative yield (entry 6).

The previously synthesized 1,4-dibenzylpiperazine could also be prepared from benzylamine and ethylene glycol (entry 7) in the absence of a solvent. After the reaction mixture had cooled to room temperature the product crystallized. The only required work-up consisted of filtration and washing with water to obtain the product in excellent yield and purity.

Several additional substrates were tried (scheme 11), but in most cases only trace amounts of product were observed by GC-MS. 1-Phenylethane-1,2-diol and benzylamine gave the mono-aminated intermediate in 67 % yield, but this did not react any further. Using higher reaction temperatures resulted in decomposition of the substrates.



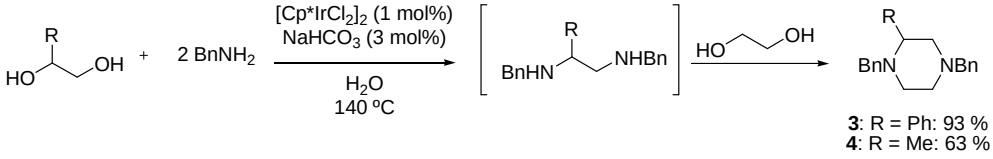
Scheme 11: Other substrates tested in the Ir-catalyzed piperazine synthesis. Only intermediates or trace amounts of product were observed.

In the experiment with 1,2-diaminobenzene the color of the mixture changed immediately when the diamine was added. This indicates that the diamine interacts with the metal center, and this can account for the low reactivity in this case.

The reaction with *N*,*N'*-dimethylethylenediamine with ethylene glycol at 170 °C did lead to more product (observed by GC-MS and in the crude NMR spectra), but a considerable degree of decomposition had also taken place. *N*-Phenylethylenediamine and L-leucinol also led to trace amounts of the products, but several by-products were observed by GC-MS. This was the result both at 110 and 170 °C. The iminosugar resulted in no conversion.

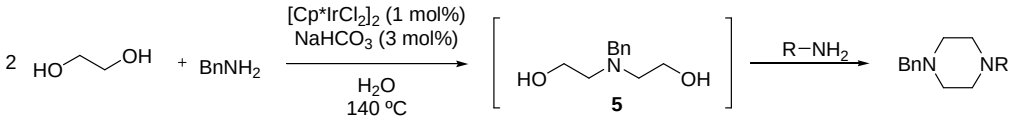
1,2-Diols are more abundant than 1,2-diamines and as we have already shown (table 4, entry 7) ethylene glycol reacts with benzylamine to form the corresponding piperazine in high yield. We now reasoned that is should be possible to react a diol with two equivalents of an amine to generate a diamine. This could in turn be reacted with a different diol to generate a piperazine (scheme 12). This strategy did indeed work, and two 1,2,4-trisubstituted piperazines **3** and **4** were prepared from easily available starting

materials. The lower yield for **4** (R = Me) resulted from incomplete conversion in the first step which led to a mixture of products.



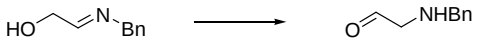
Scheme 12: 1,2,4-trisubstituted piperazines synthesized from mono-amines and two 1,2-diols.

Performing a reaction with one equivalent of benzylamine and two equivalents of ethylene glycol did not lead to the diol intermediate **5** in acceptable yield (scheme 13). We had hoped that ethylene glycol would be more easily oxidized than the 2-aminoethanol intermediates (**5** and *N*-benzylethanolamine), and that this would lead to the formation of the desired intermediate, which could in turn be converted into unsymmetrically 1,4-disubstituted piperazines.



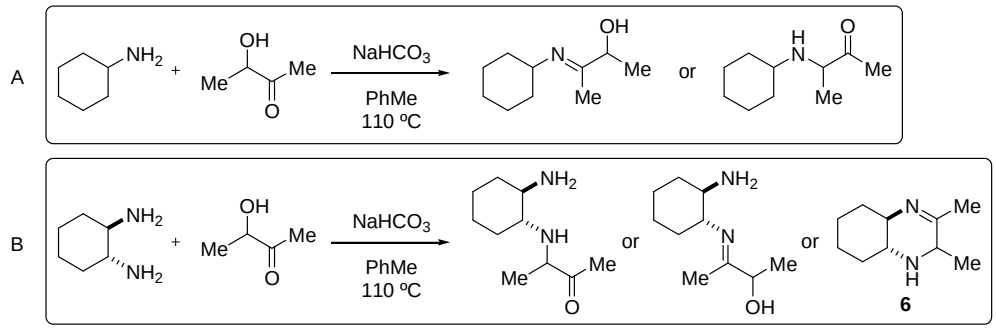
Scheme 13: Attempted synthesis of unsymmetrically 1,4-disubstituted piperazines.

One explanation why the intermediate was not form could be that the imine intermediate undergoes a Voigt reaction[29] and immediately generates an α-amino ketone which can undergo further condensation before the reduction (scheme 14).



Scheme 14: Possible Voigt reaction of the imine intermediate.

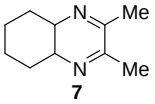
To test if the Voigt reaction plays a role under these reaction conditions, 3-hydroxy-2-butanone was heated in toluene in the presence of $NaHCO_3$ and (a) cyclohexylamine or (b) (±)-*trans*-1,2-diaminocyclohexane (scheme 15).



Scheme 15: Experiments indicated that α-hydroxy imines form α-amino ketones under the reaction conditions.

After cooling to room temperature and removal of the solvent the residue was analyzed by ^{13}C NMR. From the experiment with cyclohexylamine a small signal at 163.1 ppm was observed indicating that some imine remained. However, a much larger signal was present at 212.5 ppm, indicating that the Voigt reaction had taken place.

The other experiment showed a simple ^{13}C NMR spectrum with shifts at 159.0, 58.8, 33.4, 25.5 and 23.0 ppm. MS analysis gave a mass of 164. The interpretation of this result is that the Voigt reaction had occurred followed by condensation and that the resulting cyclic imine **6** was oxidized to the diimine **7** (figure 2).

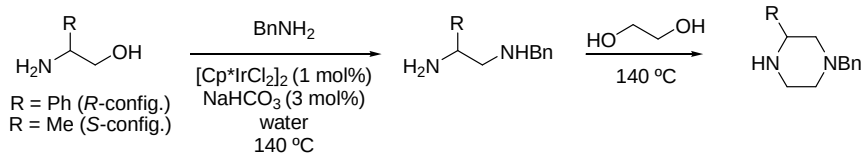


7

Figure 2: Product from reaction in Scheme 15B.

The reaction was then repeated at room temperature under an inert atmosphere. This time the ^{13}C NMR was more complex and several signals in the typical imine range were observed. The reaction mixture was then analyzed by GC-MS and the mixture was found to be mainly composed of starting materials and the cyclic imine **6** (scheme 15). These results show that the Voigt reaction takes place even at room temperature, and therefore it can be assumed to be dominating during the iridium catalyzed reactions.

An approach to useful unsymmetrically substituted piperazines with different *N*-substituents is outlined in scheme 16. Chiral ethanolamines are easily available from amino acids and would then make a good starting point for the synthesis of chiral piperazines. Furthermore, this approach would lead to a system containing one alkylated and one free nitrogen, which is useful for further modifications.



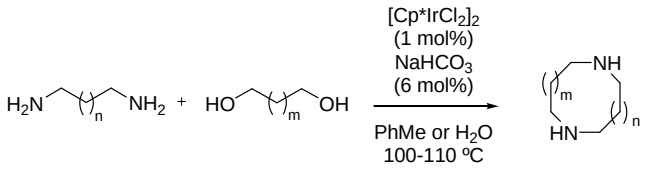
Scheme 16: Attempted synthesis of 1,3-disubstituted piperazines.

Unfortunately, the reaction did not work well. For R = Ph the product was observed by GC-MS, but several other compounds were also observed. This could be due to the fact that two different primary amines compete in the first step, and this could lead to numerous products. For R = Me the desired product was not detected.

At this point we decided to leave the piperazines, and move on to investigate the possibility of synthesizing other *N*-heterocycles by similar methods. The results from this part of the project were published in Chemical Communications.[30]

2.4.2 Synthesis of 7- and 8-menbered diamines

We then turned our attention to other *N*-heterocyclic systems. The first choice was seven and eight membered cyclic diamines using the optimized reaction conditions developed for the piperazine synthesis. Various substrate combinations were tested (table 5).



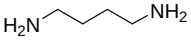
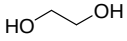
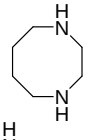
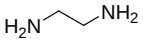
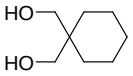
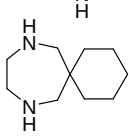
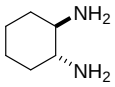
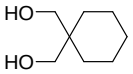
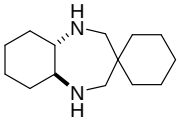
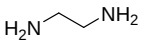
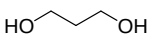
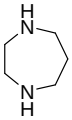
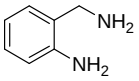
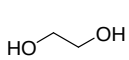
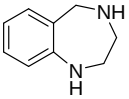
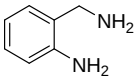
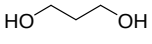
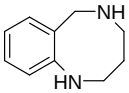
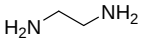
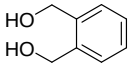
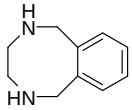
Entry	Diamine	Diol	Expected Product	Results
1				Some conv. Trace product. Several by-products.
2				Desired product was not observed.
3				Desired product was not observed.
4				Poor conversion. Multible products.
5				Low conversion. Trace of product.
6				One *N* alkylated. No ring closure
7				No conversion.

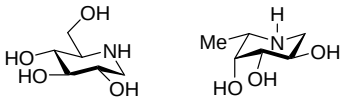
Table 5: Attempts to synthesize 7- and 8-membered diamines.

In some cases (entries 1, 4, and 5) the desired product was observed by GC-MS but only in small quantities and always as part of a complex mixture. The more complex diols in entries 2, 3, and 7 did not form the desired product. The experiment in entry 6 led to an intermediate that had been alkylated on one nitrogen atom but did not close to form the 8-membered ring. In the last case no conversion of the starting materials was observed. In the cases where traces of product were observed the experiments were performed again at 170 °C. However, this did not increase the yield, but more by-products were formed. It is interesting to notice that 1,2-diols gave product to some extent, while 1,3- and 1,4-diols did not lead to any observable product formation. The 1,2-diols can react through the Voigt reaction and thereby the reaction is less demanding for the catalyst. The other diols

do not have this possibility and the consequence seems to be poorer results. Due to the poor results with the synthesis of 7- and 8-membered diamines this part of the project was discontinued.

2.4.3 Synthesis of iminosugars

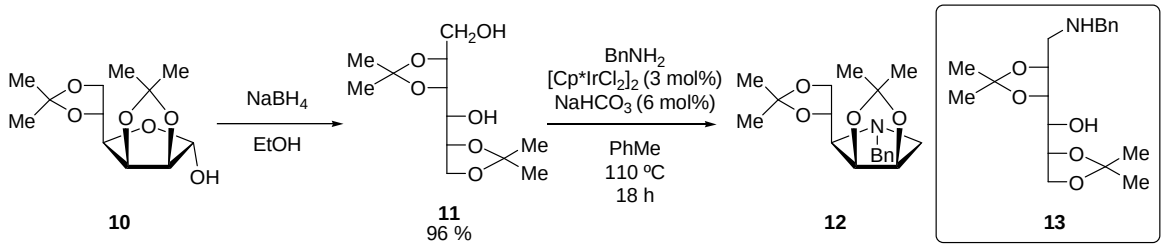
The iminosugars[31] are another group of biologically active cyclic amines that could potentially be synthesized by the iridium catalyzed *N*-heterocyclization. 1-Deoxynojirimycin (**8**) and L-1-deoxyfuconojirimycin (**9**), two of the most important iminosugars, are both potent glycosidase inhibitors (figure 3).[31b]



8 **9**

Figure 3: Two of the most important iminosugars.

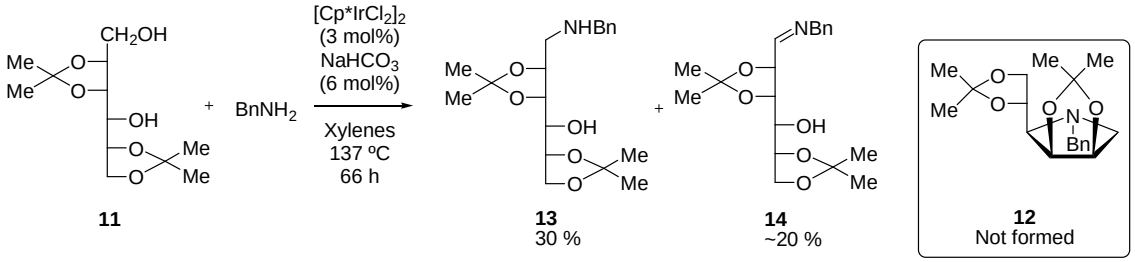
We planned to use diols that are readily available from partially protected pentoses or hexoses as substrates. The strategy is exemplified with a D-mannose derivative in scheme 17.



10 **11** 96 % **12** **13**

Scheme 17: Strategy for synthesis of iminosugars.

The commercially available mannofuranose **10** was reduced with $NaBH_4$ to give the diol **11** in 96 % yield.[32] The iridium catalyzed cyclization was then attempted with benzylamine, but the desired iminosugar **12** was not formed. Instead, the intermediate **13** was isolated in 14 % yield and 64 % of the starting material was recovered. Only the primary alcohol group had reacted, probably due to steric hindrance around the secondary alcohol. To force the reaction it was then repeated in xylenes at 137 °C for 66 hours. This increased the yield of **13** to 30 % along with ~20 % of the imine **14** (scheme 18).



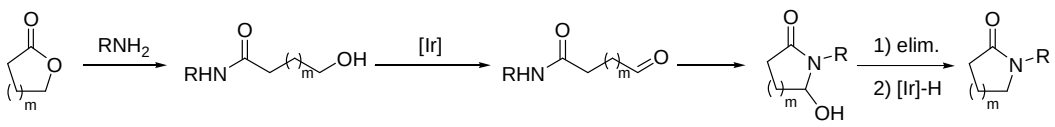
Scheme 18: The attempted synthesis of 12 led only to the intermediates 13 and 14.

Some of the diol was recovered, but much had decomposed due to the elevated temperature. The reaction was also carried out in dioxane because the solubility was found to be better in this solvent. This resulted in 13 % of **14** and 85 % of recovered **11**. Substituting $NaHCO_3$ with NaOAc gave the same result (14 % **14**; 83 % **11**). Prolonging the reaction time did not lead to further conversion. Switching to diglyme as the solvent and increasing the temperature further to 162 °C resulted in a black tar containing roughly 10 % of **14** and multiple compounds that could not be identified. This experiment was also performed with NaOAc and again in the absence base, but no improvement was observed. Due to the difficulties with these unreactive substrates this part of the project was abandoned.

2.4.4 Synthesis of lactams from lactones

Lactams are yet another group of industrially important *N*-heterocycles. The most famous examples are the β-lactam family of antibiotics[33] and caprolactam, the latter being an intermediate in the production of nylon.[34] Lactams are typically synthesized from amino acids,[35] by Beckmann rearrangement,[36] or by the Schmidt reaction.[36a,37]

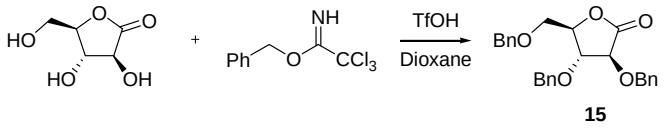
We proposed that lactams could be synthesized from a lactone and an amine (or ammonia) in the presence of the iridium catalyst. The mechanism would proceed via aminolytic ring-opening, oxidation of the alcohol, ring-formation and reduction (scheme 19). Although amides are poor nucleophiles[38] we hoped that the intramolecular nature of the reaction would render it favorable.



Scheme 19: Formation of lactams from lactones.

Alternatively, hemiacetals could be used with hydroxylamine as the nitrogen source. This would initially form an oxime, which could undergo Beckmann rearrangement to the amide by a route similar to that recently described by Williams and co-workers.[39] The resulting amide could then react as in scheme 19.

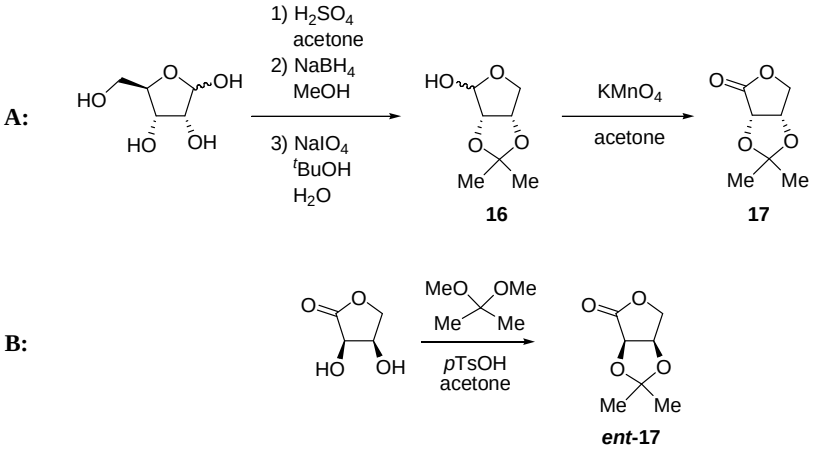
We planned to use simple unsubstituted lactones for the optimization studies, but two more complex lactones were prepared in order to determine whether the method would be applicable to more elaborate substrates. A benzyl protected arabinonolactone (**15**) was prepared by benzylation (scheme 20).[40]



15

Scheme 20: Preparation of the benzyl protected lactone 15.

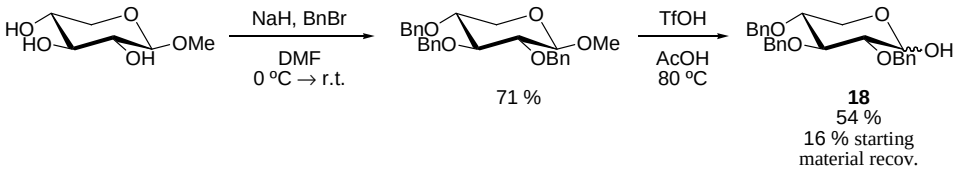
The other lactone was initially prepared from D-ribose by a multi-step route as described in scheme 21A.[41] Hemiacetal **16** was synthesized in 59 % yield (over three steps), but the final oxidation to the lactone **17** resulted in a mere yield of 12 %. Because of the low yield it was decided to use **16** for the Beckmann rearrangement/cyclization reaction. D-Erythronic acid-γ-lactone was then used to prepare ***ent*-17** in one step in 91 % yield (scheme 21B).[42]



Scheme 21: Synthesis of lactones 17 and *ent*-17.

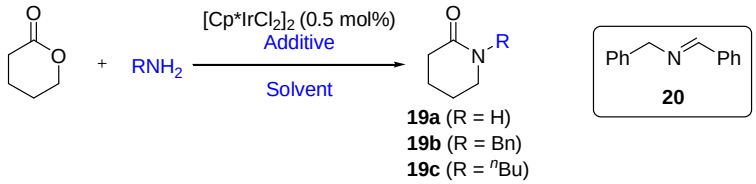
As a suitable hemiacetal substrate for the intended Beckmann rearrangement/cyclization we also prepared benzylated xylopyranose **18** (scheme 22).[43] We planned to use

hemiacetals **16** and **18** as substrates because the simple hemiacetal 2-hydroxytetrahydrofuran is known to be unstable,[44] and was not likely to be a suitable substrate in reactions at elevated temperatures.



Scheme 22: Synthesis of the xylopyranoside 18.

The initial experiments for the Ir-catalyzed lactam synthesis were performed with δ-valerolactone, ammonia and various additives in water or toluene (table 6, entries 1–5).



Entry	R	Additive	Solvent	Temp. (°C)	Yield (%)	Comments
1	H[a]	$NaHCO_3$	Water	100	trace	
2	H[a]	TFA	Water	100	-	No conv.
3	H[b]	$NaHCO_3$	Water	100	trace	
4	H[a]	$NaHCO_3$	PhMe	110	trace	
5	H[b]	$NaHCO_3$	PhMe	110	trace	
6	H[a]	$NaHCO_3$	Water	140	trace	Traces of product + by-products
7	H[a]	$NaHCO_3$	PhMe	140	trace	Traces of product + by-products
8	Bn	$NaHCO_3$	PhMe	110	~10[c]	Clean but slow conv.
9	Bn	Cs_2CO_3	PhMe	110	~10-15[c]	Multiple by-products incl **20**
10	Bn	KOH	PhMe	110	~10-15[c]	Multiple by-products incl **20**
11	Bn	TFA	PhMe	110	~10[c]	Low conv. **20** is major prod.
12	Bn	$NaHCO_3$	Water	140	38[d]	By-products; lactone remaining
13	Bn	$NaHCO_3$	PhMe	140	29[d]	By-products; lactone remaining
14	^{n}Bu	$NaHCO_3$	Water	140	~20[c]	Complex mixture

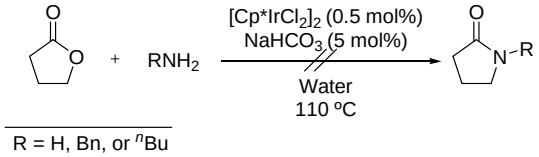
a: aq. NH_3. *b*: NH_4Cl. *c*: GC yield. *d*: Isolated yield.

Table 6: Ir-catalyzed synthesis of lactams.

When aqueous ammonia or ammonium chloride were used as nitrogen source under standard conditions, GC-MS analysis showed only trace amounts of the desired lactam **19a**. Increasing the temperature to 140 °C did not result in better yields of the lactam, but

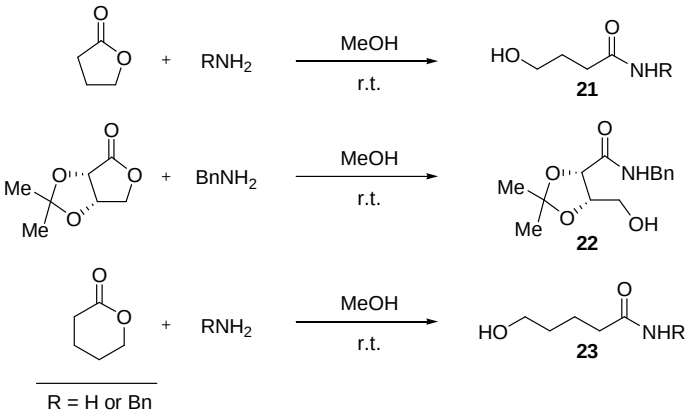
several by-products were observed (entries 6–7). Replacing the ammonia with benzylamine resulted in higher conversion, however, it remained far from complete. Using $NaHCO_3$ in toluene at 110 °C, the reaction was almost clean (entry 8), while other additives (Cs_2CO_3, KOH and TFA) resulted in slightly better conversion, but also in formation of several by-products (entries 9–11). The imine **20** was the most predominant by-product. The temperature was again increased to 140 °C and this combination gave **19b** in 38 and 29 % isolated yield with water and toluene as solvent, respectively (entries 12–13). Some starting material remained, but numerous by-products, including the debenzylated product, had also formed. Applying the most successful reaction conditions to the reaction between *n*-butylamine and valerolactone, the desired product was obtained in about 20 % yield (by GC-MS) as part of a complex mixture.

Reacting γ-butyrolactone with ammonia, benzylamine, or *n*-butylamine in water gave only small amounts of the corresponding lactams (as observed by GC-MS) along with some by-products (scheme 23).



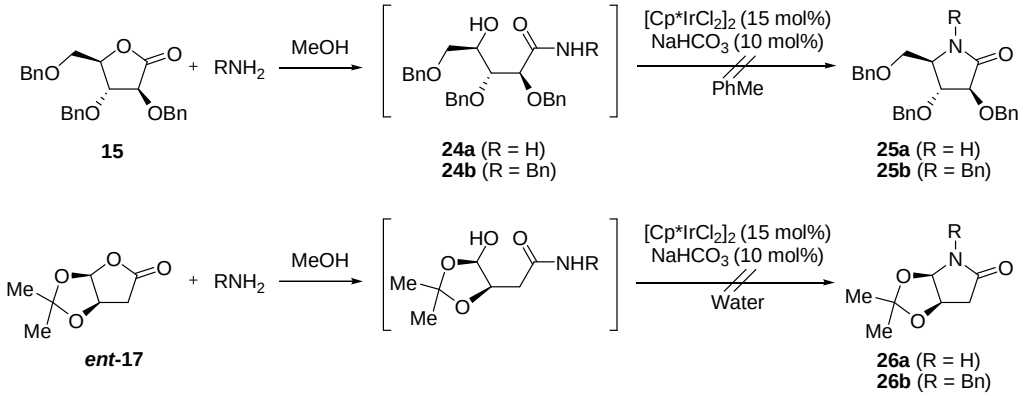
Scheme 23: Attempted synthesis of lactams from γ-butyrolactone.

It seemed that it was not possible to obtain good yields of the lactams simply by varying the reaction conditions. It is known that aminolysis of lactones can be a slow process[45] but can be catalyzed *e.g.* by sodium 2-ethyl hexanoate.[46] To test if the poor conversion was a result of slow aminolysis several lactones were subjected to different amines or ammonia (scheme 24), and it was observed that the aminolysis took place even at room temperature, and reaching complete conversion required 2–3 hours depending on the reactants.



Scheme 24: Aminolysis of three lactones with benzylamine or ammonia.

The amides **21** and **23** were observed by GC-MS, while **22** was characterized by NMR. A sequential procedure was then tested. First a lactone was treated with ammonia or benzylamine in methanol until TLC analyses indicated complete conversion. The solvent was then removed *in vacuo* and the residue[b] was dissolved in water or toluene along with the iridium catalyst and $NaHCO_3$, and heated to 100 (water) or 110 °C (PhMe) for 24 hours (scheme 25).

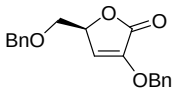


Scheme 25: Attempted synthesis of lactams by sequential aminolysis and ring closure.

Analysis of the reaction mixture showed complex mixtures in the case of **25b**, **26a** and **26b**. The desired lactams could not be observed in the NMR spectra of the crude mixtures. Separation by column chromatography gave neither the desired product nor starting material. In the case of **25a** some starting material was recovered along with another compound, which was proposed to be **27** based on NMR analysis (figure 4). The

[b] For **24a** a sample was analyzed by IR and no lactone-bands were observed. Typical primary amide absorptions were observed: 3468, 3350, and 1671 cm^{-1} indicating that **24a** had formed.

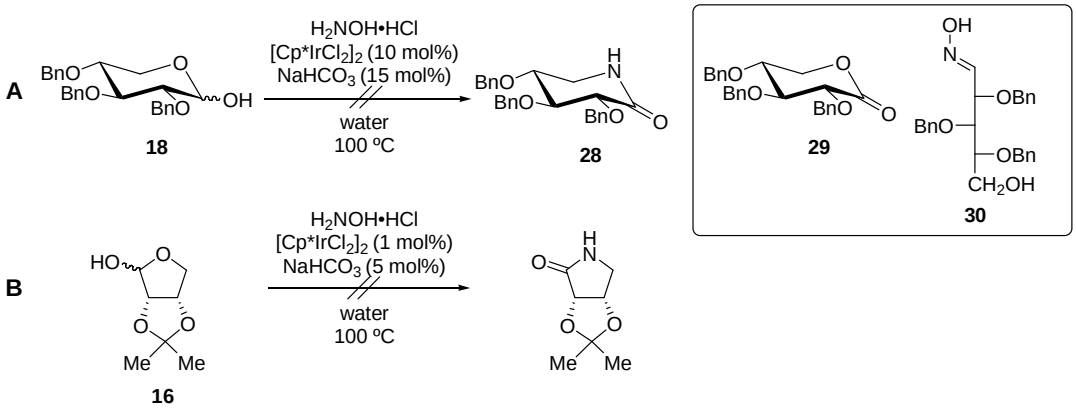
elimination of OBn groups from lactones or hemiacetals have been reported to occur in the presence of either palladium catalysts[47] or strong bases.[48]



27

Figure 4: Proposed structure of the isolated by-product.

Despite the poor results with the lactamizations, the Beckmann rearrangement/cyclization reaction was attempted on the hemiacetals **16** and **18** (scheme 26).



Scheme 26: Attempts to prepare lactams by a Beckmann rearrangement/cyclization sequence.

In the case of **18** none of the desired lactam **28** was observed. When a catalytic amount of base was used the major product (37 %) was the corresponding lactone **29**.[c] When excess base was used to free the hydroxylamine a different compound was formed preferentially. Based on ^{13}C NMR and supported by literature precedence[49] the structure of this compound is proposed to be aldoxime **30**. The reaction with hemiacetal **16** resulted in a black tar from which no product could be extracted.

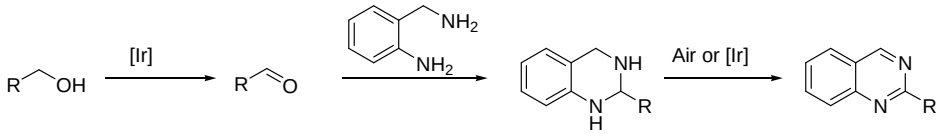
Based on the findings that aminolysis was not the reason for the poor results, and that lactones of moderate complexity were decomposed under the reaction conditions we reasoned that the present catalyst system was not likely to overcome these problems. As a result the lactamization was not pursued any further.

[c] Structural assignment based on ^{13}C NMR and IR which showed a characteristic 6-membered lactone band at 1751 cm^{-1}.

2.4.5 Synthesis of pyrazine, quinazoline and related N-heterocycles

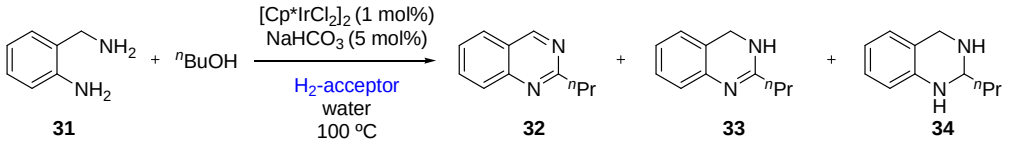
Aromatic diamines such as pyrazines and quinazolines[50] are another group of pharmaceutically important heterocycles. One way to synthesize quinazolines is a condensation between an aldehyde and a 2-aminobenzylamine followed by oxidation. This oxidation can be accomplished by DDQ,[51] air/TFA, or air/activated carbon (Darco® KB).[52]

We imagined that treating a primary alcohol with the iridium catalyst would give an aldehyde that would *in situ* condensate with a 2-aminobenzylamine to give a 1,2,3,4-tetrahydroquinazoline. This could then be oxidized to the corresponding quinazoline by air or by aid of the catalyst (scheme 27).



Scheme 27: Synthesis of quinazolines from alcohols and 2-aminobenzylamines.

The active iridium complex could be regenerated either by release of H_2 or by reduction of a sacrificial H_2-acceptor.[53] The former would obviously be the more attractive option from an atom-economy point of view, but also the more demanding for the catalyst. For this reason we decided to start with the less demanding route using a H_2-scavenger. Therefore benzophenone, di-*tert*-butyl ketone and cyclohexene were all tried as H_2-acceptors in the reaction between 2-aminobenzylamine and 1-butanol (table 7).



31 **32** **33** **34**

Entry	H_2-acceptor	Result
1	Ph_2CO (1 equiv)	Primarily **34**
2	Ph_2CO (5 equiv)	17 % **32** (isolated)
3	$^tBu_2CO$ (1 equiv)	Minor: **32**; Major: **31**
4	$^tBu_2CO$ (5 equiv)	Minor: **32**; Major: **31**
5	Cyclohexene (2 equiv)	Mix. of **32, 33, 34**
6	none[a]	~1:1:1 of **32:33:34**

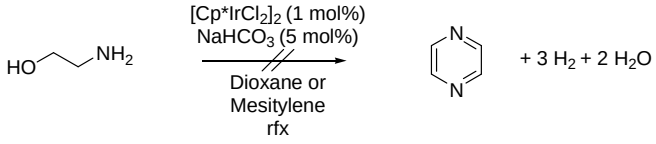
a: Performed at 140 ºC

Table 7: Screening of various H_2-scavengers in the preparation of quinazolines.

With one equivalent of benzophenone (entry 1) the saturated analogue **34** was the major product (by GC-MS), and only small amounts of **32** and diphenylcarbinol were observed. Increasing the amount of benzophenone to 5 equivalents gave **32** as the major product (GC-MS) but only 17 % was isolated after column chromatography (entry 2). Di-*tert*-butyl ketone resulted in low conversion of **31** with only trace amounts of **32** formed (entries 3–4). Cyclohexene and absence of H_2-acceptor led to complete conversion into a mixture of **32**, **33** and **34** with only minor impurities (entries 5–6). Increasing the temperature did not give better results.

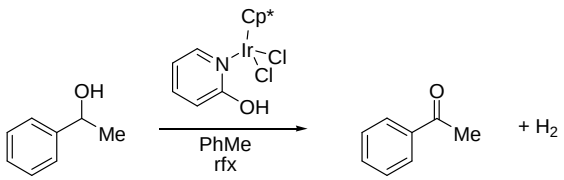
The reaction was also performed in toluene (with benzophenone as the H_2-scavenger) but again low conversion into **32** was observed. Prolonged reaction times (up to 3 days) led to improved the conversion (GC), however, NMR analysis showed a much more complex mixture, indicating that decomposition was a major problem under these reaction conditions.

To explore the possibility of preparing aromatic *N*-heterocycles without sacrificial H_2-scavengers we first examined a somewhat simpler system, namely the dimerization of ethanolamine to form pyrazine (scheme 28).



Scheme 28: Attempted synthesis of pyrazine by release of hydrogen.

The desired product was not observed, even at increased temperatures (refluxing mesitylene). After these experiments had been carried out, Yamaguchi and co-workers published a new catalyst for oxidation of alcohols with ligand assisted release of hydrogen (scheme 29).[54]

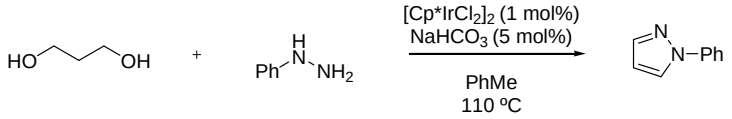


Scheme 29: Yamaguchi's method for oxidation by H_2 release.

While useful for the oxidation of simple alcohols we predicted that the essential pyridine ligand would not remain coordinated in the presence of ethanolamine or diamine substrates, and therefore this procedure was not tried in our case.

2.4.6 Synthesis of pyrazoles

Finally, we wanted to investigate the possibility of preparing pyrazoles from 1,3-diols and hydrazines (scheme 30).



Scheme 30: Synthesis of pyrazoles from 1,3-diols and hydrazines.

In order to drive the reaction to completion an open system was used to allow the hydrogen gas formed to escape from the reaction mixture. Initially, some pyrazole was formed and the build up of an intermediate was observed by GC-MS. However, conversion stopped after 2–3 hours. The reaction was repeated with 3-pentanone as a hydrogen scavenger, but the ketone reacted as an *N*-alkylating reagent instead. Using water as the solvent led primarily to the formation of the saturated pyrazolidine, whereas mesitylene (at reflux temperature) gave a better conversion into the desired pyrazole. After column chromatography 1-phenyl pyrazole was collected as a red oil that contained the partially reduced 4,5-dihydro-1-phenyl-1*H*-pyrazole as an impurity (yield ~35 %). A similar result was obtained when the reaction was performed neat at 140 ˚C.

At this point the project was taken over by Paw Jensen as part of bachelor project. He varied reaction temperatures, solvents, additives (bases or acids), and obtained yields between 6 and 17 %. The best result was obtained by running the reaction neat at 140 °C with a catalytic amount of TFA. However, in all cases he found that formation of aniline was faster than the desired reaction, and it seemed that suppressing this side reaction was not possible. With this conclusion the pyrazole synthesis was abandoned.

2.4.7 Search for a new catalyst

Apart from the piperazine part of the project the results were not satisfying. This was largely attributed to the low activity of the catalyst that forced us to use harsh reaction

conditions that in turn led to side reactions and decomposition. It was then clear that a more active catalyst was needed to render these reactions feasible. While ruthenium[55] and other metals are widely used in transfer hydrogenation, iridium has been the most successful in the reduction of imines.[56] Therefore we decided to focus on iridium in our search for more efficient catalysts for the intended heterocycle syntheses. The modification of the Cp*Ir(III) scaffold was thought to be difficult since the Cp* ligand leaves only few coordination sites open to other ligands. This is especially relevant if the entire reaction takes place on the metal and both alcohol and amine must remain coordinated throughout the catalytic cycle. Additionally, the high concentration of amine could out-compete many other ligands. A number of known Cp*Ir(III) complexes with bidentate ligands were prepared (figure 5; **35**–**39**) since these ligands could probably remain coordinated to the metal even in the presence of amine substrate. The Cp* ligand itself is not easily modified. Other cyclopentadienyl ligands have been reported, but these are either expensive or must be synthesized by multi-step sequences. One exception is the indenyl-ligand and Ir(I) complex **43** was synthesized (*vide infra*) and oxidized to the corresponding Ir(III) by treatment with I_2 prior to use.[57] Other interesting catalyst candidates were found in the literature describing the reduction of imines. We focused on this reaction type since this part of the catalytic cycle was thought to be more challenging than alcohol oxidation. Several Ir(I)COD complexes are known to reduce imines at room temperature. These are most often Ir(I) complexes containing bidentate phosphine ligands[56,58] (like complex **44**) or various *P,N*-ligands.[59] Unfortunately, the described substrate scope for imine reductions are often limited to benzylic imines of anilines, and it was difficult to predict if these catalysts would be applicable to *e.g.* the piperazine synthesis. Finally, the (*R*)-^{i}Pr-PHOX ligand developed by Pfaltz was chosen as a representative *P,N*-ligand (generating Ir(I)-PHOX complex **45**) for its commercial availability. The non-coordinating BAr_F-anion has been shown to be essential for activity in reduction of imines with similar Ir-complexes.[56] Shvo's catalyst **46** is also known to catalyze transfer hydrogenation reactions involving imines.[60] This complex is commercially available and was also included in the catalyst screening. The catalysts tested are shown in figure 5.

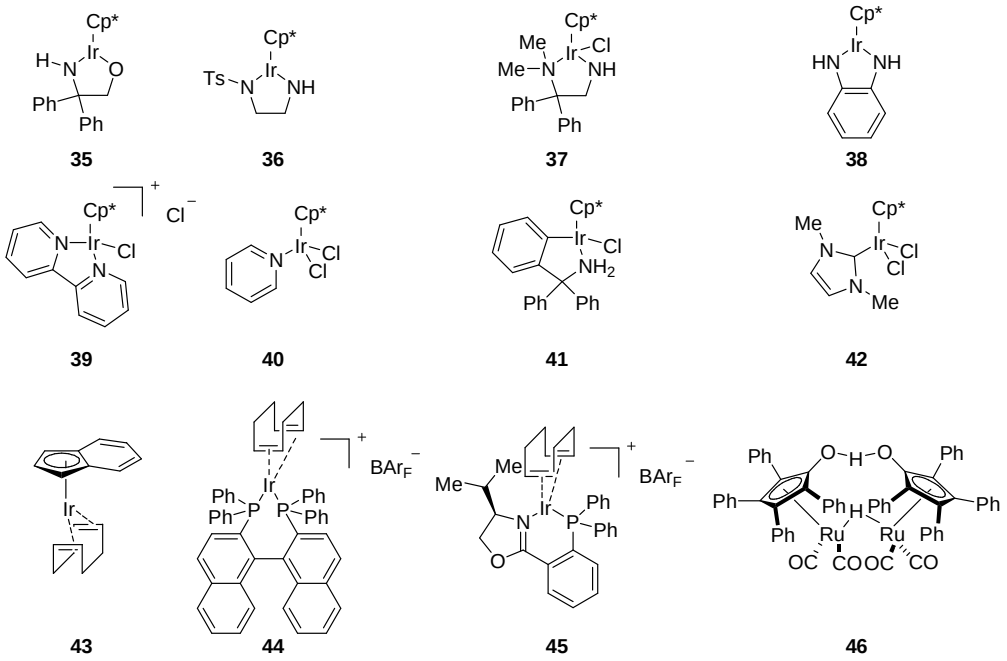
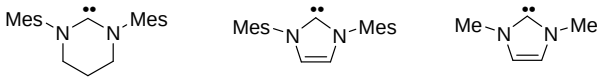


Figure 5: Ir and Ru complexes tested in this study.

Complexes **35**–**38** were synthesized by treating $[Cp^*IrCl_2]_2$ with the appropriate diamine or 1,2-ethanolamine in the presence of a base. The complex **38** was prepared *in situ*, while the complexes **35**–**37** were prepared in a separate reaction vessel, and the crude products used directly after extraction and drying. The ligands were either commercially available or synthesized by known procedures (see experimental section). The complexes **39**[61] and **40**[62] were prepared in a similar fashion with (bi)pyridine but no base. Iridacycle **41** was prepared from tritylamine by a known procedure.[63] The corresponding amido complex[d] was not stable under normal isolation conditions, and was therefore prepared *in situ* when tested as a catalyst. The analogue prepared from benzylamine was found to be unstable, and could not be isolated in pure form. The Ir(I) complex **43** was synthesized from freshly prepared potassium indenide and $[Ir(COD)Cl]_2$.[64] Complexes **44** and **45** were synthesized from $[Ir(COD)Cl]_2$, $NaBAr_F$ and (±)-BINAP,[65] or the PHOX ligand[66] respectively.

The synthesis of the Ir-NHC **42** complex turned out to be the most problematic. Initially, three NHC ligands were targeted (figure 6).

[d] Obtained by treating **41** with ^{t}BuOK in CH_2Cl_2.

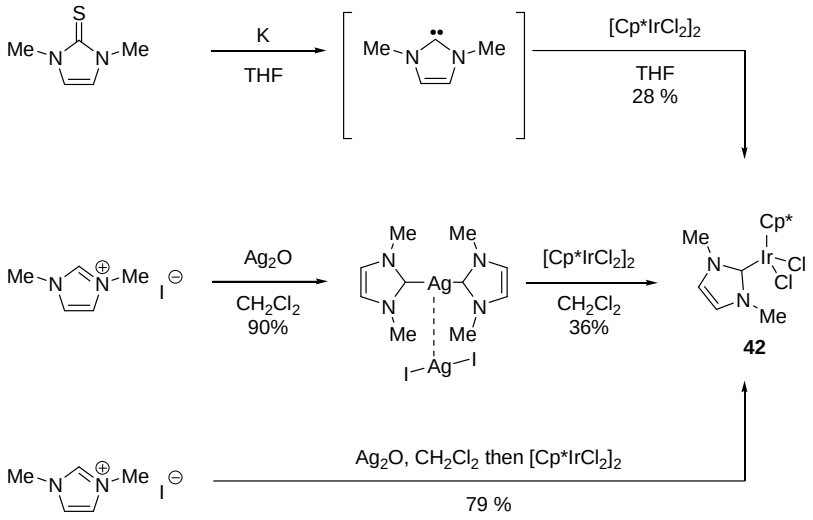


47 48 49

Figure 6: NHC ligands for Ir complex formation.

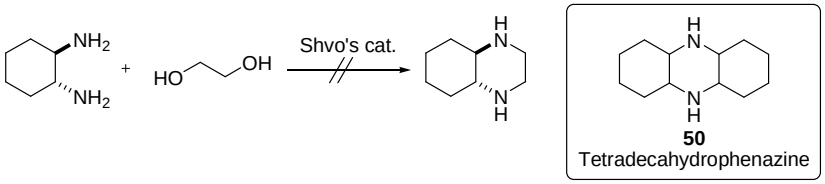
Numerous methods have been developed for the synthesis of NHC metal complexes.[67] The most straight forward method for forming NHC-metal complexes is generation of the free carbene by deprotonation of the appropriate imidazolium salt followed by addition of the metal. Alternatives include generation of the free carbene by reductive desulfurization of *N*,*N*′-dialkylthioureas,[68] liberation of carbenes from air and moisture stable *N*,*N*′-disubstituted imidazolium-2-carboxylates[69] and NHC transfer from stable silver(I) NHC complexes.[70] Deprotonation of imidazolium salts by NaH and a catalytic amount of ^{t}BuOK[e] proceeded at a reasonably fast rate, but when the carbene solution[f] was added to $[Cp^*IrCl_2]_2$ no product was obtained. The imidazolium-2-carboxylate strategy was also attempted, but again no Ir-NHC complex could be obtained. Reductive desulfurization of the 1,3-dimethyl thiourea derivative followed by treatment with the Ir-dimer gave the corresponding Ir-NHC complex in 28 % yield (scheme 31). The silver transmetallation route gave 36 % yield when the intermediate was isolated. Generation of the silver(I)-NHC complex immediately followed by addition of the iridium source without prior purification gave the desired compound in 79 % yield. Due to difficulties in preparing the Ir-NHC complexes the two other ligands were abandoned.

[e] Without ^{t}BuOK the deprotonation proceeded very slowly.
[f] Obtained by filtration of the reaction mixture using Schlenk technique.



Scheme 31: Different approaches to Ir-NHC complex 42.

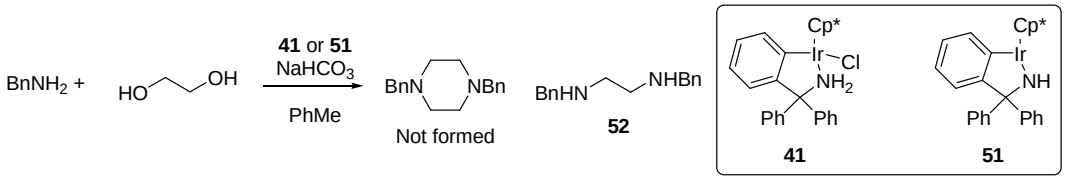
With a wide range of iridium complexes in hand we now tested these as potential catalysts in the *N*-heterocycle synthesis described above. Being perhaps the least demanding, the reaction between ethylene glycol and *trans*-1,2-diaminocyclohexane was chosen as the model reaction. In most cases no conversion was observed. Exceptions are **40**, **41** and **45** which all gave the desired product, albeit in very low yield. With **37** almost complete consumption of the starting materials was observed but the desired product was only isolated in 36 % yield. Shvo's catalyst, **46**, gave good conversion, but none of the desired product was formed. GC-MS analysis indicated that the major product is tetradecahydrophenazine (**50**, scheme 32). The NMR spectra were, however, more complex, indicating that the major product was a mixture of isomers. Shvo's catalyst has been shown to catalyze the *N*-alkylation of anilines with amines,[71] and presumably, a similar reaction had taken place in our case.



Scheme 32: Proposed structure of the major product from the reaction with Shvo's catalyst.

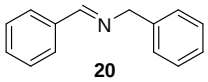
Surprisingly, neither **44**, **45** nor **46** were able to catalyze the alkylation of aniline with benzyl alcohol. All these complexes are known to hydrogenate imines of aniline, and it was assumed that the benzyl alcohol would be oxidized to benzaldehyde in all cases.[56,58,59,60]

The iridacycle **41** and the corresponding amido complex (**51,** generated *in situ* due to instability) were tested in the reaction between benzylamine and ethylene glycol (scheme 33). This reaction was chosen because the iridacycle **41** was formed easily in the presence of tritylamine and a weak base. We expected that similar iridacycles would form in alkylation reactions with benzylamines catalyzed by $[Cp^*IrCl_2]_2$.[63,72] In the reaction with **41** the intermediate **52** was observed in trace amounts and no piperazine product was formed. This result indicates that benzylamines can deactivate the catalyst by formation of iridacycles. Testing **51** as the catalyst led to no conversion of the starting material.



Scheme 33: Iridacycles 41 and 51 were not effective catalysts in the *N*-heterocyclization.

The Ir-NHC complex **42** was also used as catalyst in the reaction between benzylamine and either 1-heptanol or 1,5-pentanediol. In neither case was any conversion of the alcohol observed, but most of the amine was converted into *N*-benzylbenzaldimine (**20**, figure 7).



20

Figure 7: Major product from attempted *N*-heterocyclization with complex 42.

It is well known that the pH plays a very important role in the transfer hydrogenation reactions catalyzed by Ir(III) complexes bearing bidentate diamine[73] or bipyridine[74] ligands. The optimum pH is often between 2 and 5. The complexes **36**, **39** and **40** were therefore revisited and the reaction between 1,5-pentanediol and benzylamine (or its ammonium chloride salt) was tried at pH 3.8, 5.0 and 7.0 (performed in parallel screenings where either TFA or $HClO_4$ were used to adjust the pH). In all cases only

traces of the product were observed, and is was concluded that the poor results cannot be attributed to the pH of the solution.

Most of the complexes tested were already known to catalyze other types of hydrogen transfer reactions; however, they all failed in the alkylation of amines with alcohols. With the most promising choices for new catalysts exhausted, we expected that development of new, more active catalysts would be a challenging task, which was not possible due to time-constraints.

2.5 Conclusion

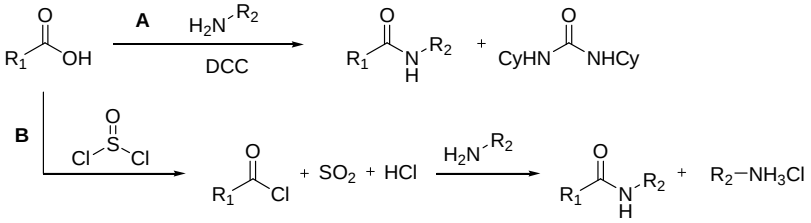
The aim of the project was to develop new methods for the preparation of *N*-heterocycles, such as piperazines, pyrazines, lactams etc. The development of a method for the synthesis of piperazines was successful, and the method is applicable to a range of substrates leading to piperazines with diverse substitution patterns. When a chiral diamine was used as substrate the optical purity was retained, and thus optically pure piperazines are available by this procedure. Piperazines could be formed from two different diols by a sequential procedure. The results obtained in this project were published in *Chemical Communications*.

The other heterocycles proved to be much more difficult to prepare. Some were met with moderate success (38 % yield of a lactam), but were found to work for only the most simple substrates. The remaining attempts to synthesize *N*-heterocycles were unsuccessful, as was the search for a new and more active catalyst. Concerning the mechanistic course of the reaction, we demonstrated that the Voigt reaction pathway is important for this type of reaction, and consequently 1,2-diols performs much better than other diols.

3 Ruthenium catalyzed synthesis of amides from alcohols and amines by extrusion of dihydrogen

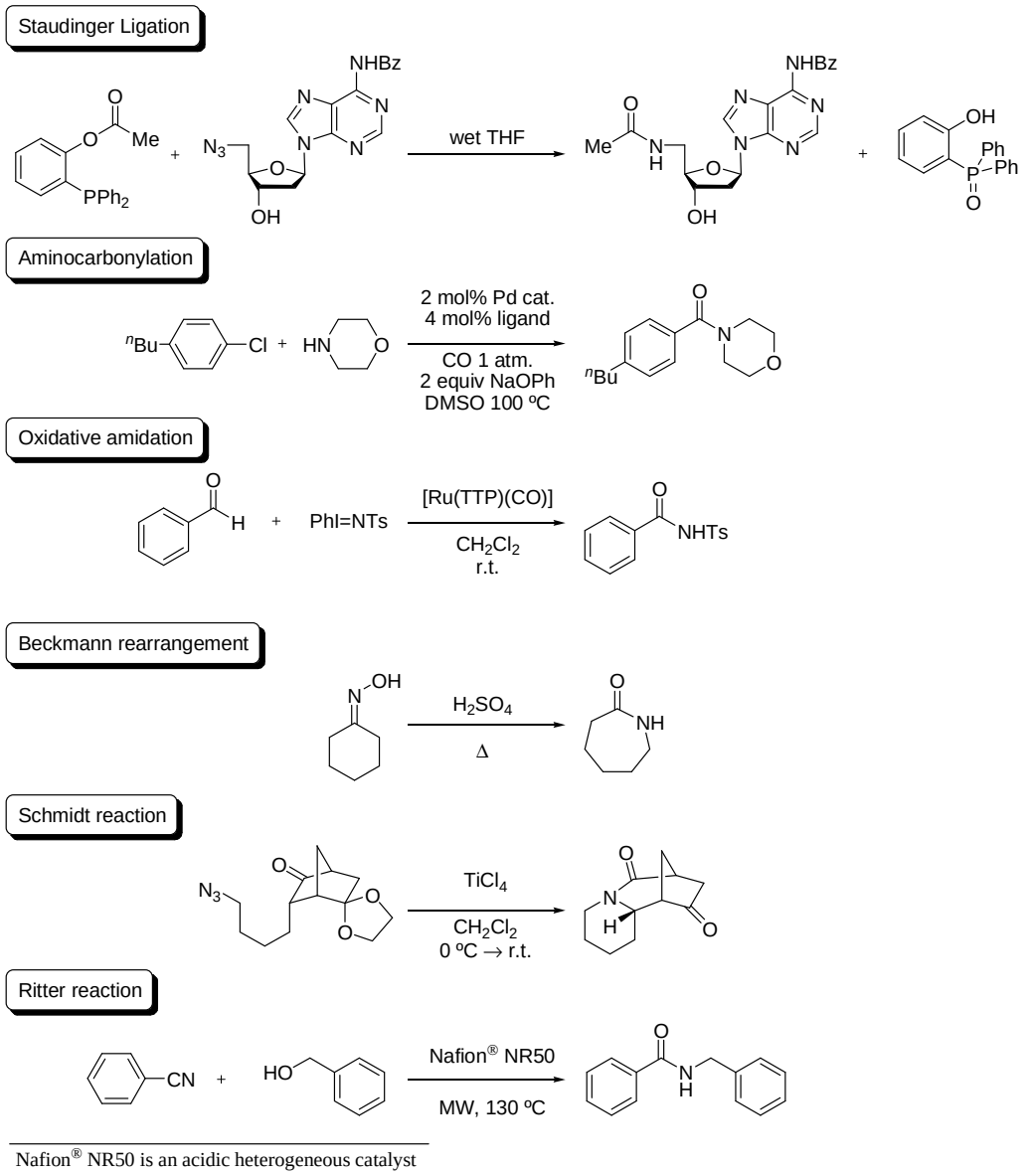
3.1 The amide bond – Importance and synthesis

The amide bond is one of the most important bond types in organic chemistry. The most famous amide bond occurs in peptides and proteins and the peptide bond is essential for all life forms. The amide functionality is also important in many non-peptide natural and industrial products, such as pharmaceuticals, polymers (*e.g.* nylon and Kevlar®) etc. The amide bond is often formed by reaction between an amine and a carboxylic acid. The acid must be activated, either *in situ* by a coupling reagent or by prior conversion into a reactive derivative, *e.g.* an acid chloride. The two methods are exemplified by a DCC coupling reaction (scheme 34A) and activation through the acid chloride in scheme 34B. In both cases, the atom economy is very poor, and large quantities of chemical waste are produced.



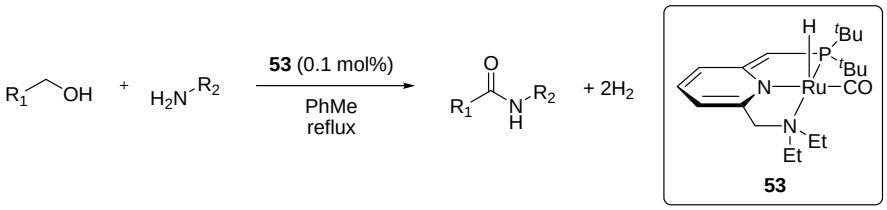
Scheme 34: Amide synthesis by DCC coupling (A) and via acid chloride (B).

Alternative methods for the preparation of amides include the Staudinger ligation,[75] aminocarbonylation of aryl halides,[76] oxidative amidation of aldehydes,[77] Beckmann rearrangement of oximes[36,78] the Schmidt reaction,[36a,37] and the Ritter reaction.[79] Examples of these reactions are shown in scheme 35.



Scheme 35: Amide synthesis can be achieved by several methods. Nafion® NR50 is an acidic heterogeneous catalyst.

Some of these alternative methods also produce stoichiometric amounts of waste (the Beckmann rearrangement, the Schmidt and the Ritter reaction are exceptions) and some require starting materials that are not readily available. This illustrates the importance of new, environmentally friendly methods for the synthesis of amides which can reduce the amount of waste produced in the chemical industry. One such method was published by Milstein and co-workers recently.[80] They used a special ruthenium-pincer complex (**53**) to form amides from alcohols and amines (scheme 36).



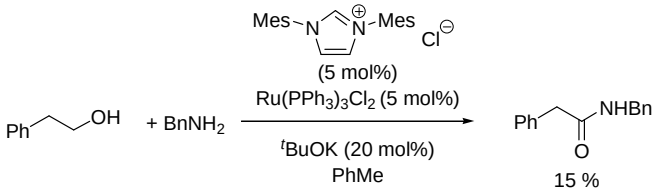
Scheme 36: Milstein's amide synthesis catalyzed by pincer complex 53.

Typically both these types of substrates are easily available. Most notably, the reaction does not require a stoichiometric oxidant since hydrogen gas is released during the course of the reaction. The drawbacks of this reaction are the relatively limited substrate scope and the complexity of the catalyst **53** which must be synthesized via a multi-step sequence. Moreover, the amidation reaction is carried out in a glove box, making it tedious to perform.

3.2 Development of an easily accessible amidation catalyst

3.2.1 Initial findings

This project was started by Dr. Henning Vogt who worked in the Madsen group as a postdoctoral research fellow. His goal was to find new ruthenium based catalysts for the alkylation of amines with alcohols. However, he observed that when an *in situ* formed Ru-phosphine-NHC[g] complex was treated with 2-phenylethanol and benzylamine the predominant product was not the expected amine but the corresponding amide (scheme 37). Much of the starting materials remained, and the only by-product was imine **20**, which was formed in ~10 % yield (estimated from GC).

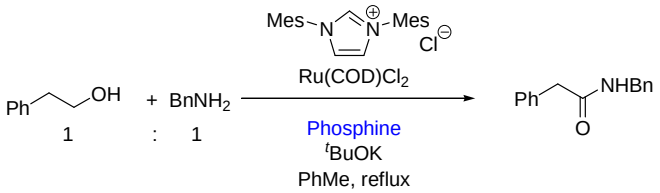


Scheme 37: The initial observation of an amide formed by a Ru-NHC catalyst.

[g] The catalyst components were stirred for 20 min. in refluxing PhMe before the substrates were added.

3.2.2 Optimization studies

It was decided that this surprising result should be followed up with optimization studies. We first focused on the phosphine ligand. Thus, the ruthenium source was changed to $Ru(COD)Cl_2$ and a wide range of phosphines and related ligands were screened (table 8).



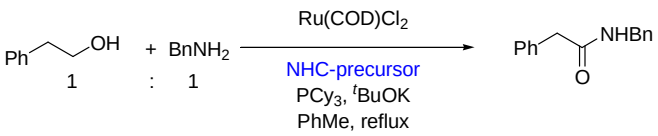
Entry	Phosphine	GC yield (%)	Entry	Phosphine	GC yield (%)
1	P^tBu_3	22	8	$AsPh_3$	24
2	P^nBu_3	9	9	dppe	0
3	$P(2\text{-furyl})_3$	26	10	dppp	0
4	PPh_3	21	11	dppb	0
5	PCy_3	27	12	dppf	0
6	$P(o\text{-tol})_3$	16	13	Pyr	12
7	$O{=}PPh_3$	24	14	none	12

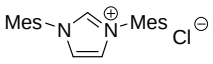
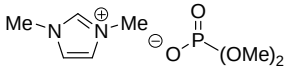
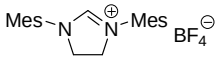
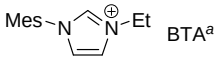
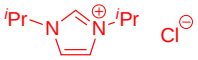
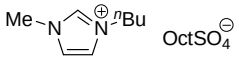
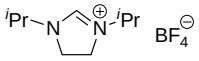
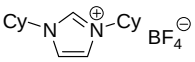
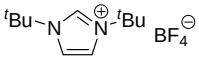
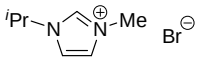
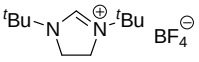
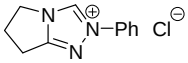
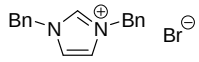
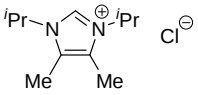
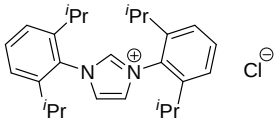
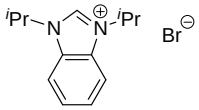
All reactions were performed with 5 mol% $Ru(COD)Cl_2$, IMes Cl, and phosphine. 15 mol% base.

Table 8: Phosphine screening for the amidation reaction.[h]

The screening showed that a phosphine with a small cone angle[81] (entry 2) gave the lowest yield. Larger cone angles led to improved yields (entries 1, 3–6) with the optimum at PCy_3. The phosphine oxide and $AsPh_3$ also gave good results (entries 7 and 8). Bidentate phosphines (entries 9–12) all resulted in no product formation. Pyridine and the absence of a ligand (except NHC) gave lower yields than the bulky phosphines. We then chose PCy_3 for the further optimization. The NHC ligand was the next subject in the screening process (table 9).

[h] Experiments carried out in collaboration with Dr. Henning Vogt.



Entry	NHC	GC yield (%)	Entry	NHC	GC yield (%)
1		24	9		53
2		45	10		24
3		92	11		92[b]
4		48	12		84
5		68	13		8
6		22	14		8
7		1	15		25
8		7	16		14

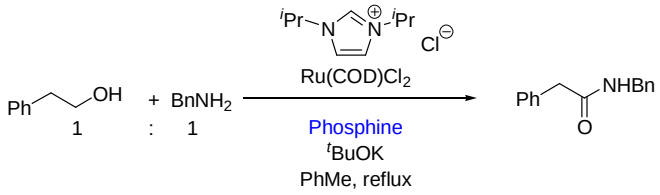
Same stoichiometry as in table 8. *a*: BTA = Bis(trifluoromethanesulfon)amide. *b*: LiCl was added.

Table 9: Screening of carbene ligands.

Some of the NHC precursors were not commercially available. Their syntheses are described in the experimental section. Changing from the NHC with an unsaturated backbone to the saturated analogue, gave an increased yield for the mesitylene substituted NHCs (compare entries 1 and 2). However, the opposite effect was observed for alkyl substituted NHCs where the unsaturated ligands performed significantly better than their saturated counterparts (entries 3–6). In entries 1 and 2 the counter ion had also been changed, which could have had an impact on the yield. When comparing entries 5 and 6 it becomes clear that the decrease in yield is not due to the tetrafluoroborate anion. NHCs with various other *N*-substituents were also examined (entries 7–13). The very bulky (2,6-diisopropylphenyl substituted) NHC gave low conversion. Simple alkyl substituents generally gave reasonable yields except for dibenzyl and unsymmetrically Me,^{i}Pr

substituted NHCs. It has been shown that the difference in reactivity of metal complexes with different NHCs can generally be attributed to steric effects of the *N*-substituents instead of electronic effects.[82] However, substitution on the NHC backbone can lead to ligands which differ significantly in their electronic properties. In order to include NHCs with a broader range of electronic influence a triazolium (entry 14) and two imidazolium salts with backbone substituents (entries 15 and 16) were tested. None of these showed any improvement over the previously tested NHCs. From the NHC screening it was concluded that the commercially available isopropyl substituted NHC (entry 3) was the ligand of choice.

At this point a fine tuning of the catalytic system by reinvestigation of the phosphine ligand seemed appropriate. This time we narrowed the screening to include ligands that were structurally similar to PCy_3. The results are shown in table 10 and the structures of the biaryl (Buchwald) ligands are shown in figure 8.



Entry	Phosphine	GC yield (%)	Entry	Phosphine	GC yield (%)
1	PCy_3	92 (46)[a]	5	DavePhos	3
2	Cy-JohnPhos	90	6	$P(Cy)_2Ph$	54
3	XPhos	13	7	$PCyp_3$	98[b] (67)[a]
4	JohnPhos	34	8	$PCyp_3$•HBF_4	92[b,c]

Same stoichiometry as in table 8. *a*: Yield after 3 hours. *b*: The isolated yields from these reactions were identical. *c*: 20 mol% base was used.

Table 10: Results from the second phosphine screening.

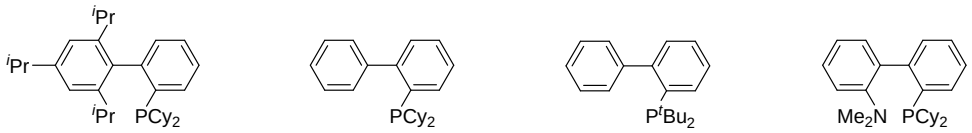


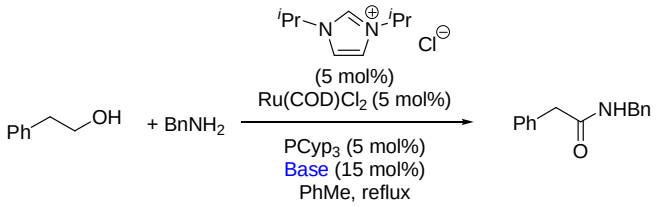
Figure 8: Structures of the Buchwald biaryl ligands.

The Cy-JohnPhos ligand gave 90 % yield (entry 2), but all the other biaryl ligands gave poor to mediocre yields (entries 3–6). Of the ligands tested tricyclopentylphosphine

($PCyp_3$) gave the best yield (98 %, entry 7). Because complete conversion was observed for both PCy_3 and $PCyp_3$ and the GC-yields were similar, the yields after 3 hours were compared, (table 10, entries 1 and 7 in parentheses), and it became obvious that $PCyp_3$ gave a significant increase in reaction rate. Since trialkylphosphines tend to be easily oxidized, the HBF_4 salts are often used as air stable substitutes.[83] In this case the $PCyp_3 \cdot HBF_4$ gave a slightly lower GC yield than the free phosphine, but the isolated yields turned out to be identical. For practical reasons it was decided to continue the studies with the HBF_4 salt.

The ratios between ruthenium and both ligands and the base were also examined, but no improvement was observed when an excess of ligands was used. With regard to the base, a minimum of 20 mol% was needed (15 mol% when the free phosphine was used). Liberation of the phosphine and the carbene accounts for 10 mol%, but the role of the remaining base is not clear. We speculated that the *N*-substituent(s) on the NHC could undergo C-H activation[84] and that the base then serves to generate a coordinatively unsaturated complex that will act as the catalyst (*vide infra*). This could result in a Ru-complex with some resemblance to Milstein's catalyst **53**. Unfortunately, it was not possible to isolate any well defined metal complex from the reaction mixture before the substrates were added.

Since the presence of a strong base would render this method incompatible with sensitive substrates we examined some weaker bases, as well as the possibility to quench any remaining base before addition of the substrates. The results are summarized in table 11.



Entry	Base	Additive[a]	GC yield (%)	Comments
1	NaOAc	-	-	By-products
2	Cs_2CO_3	-	59	Full conv. By-products
3	none	-	-	By-products
4	^{t}BuOK	H_2O	59	35 % alcohol remaining
5	^{t}BuOK	NH_4Cl	-	Low conv. Imine observed
6	^{t}BuOK	$NaHCO_3$	72	Full conv. By-products
7	Ag_2O[b]	-	-	By-products

a: Additive was added just before the substrates. *b*: Ag:NHC 1:1; Ag_2O and NHC precursor were allowed to react before Ru and $PCyp_3$ were added.

Table 11: Screening of the base and additives in the amidation reaction.

Sodium acetate, as well as absence of base (entries 1 and 3) led to complex mixtures that did not contain any of the desired amide. Cs_2CO_3 (entry 2) gave a reasonable yield but also several by-products. We then tried to preform the catalyst and quench any excess base just before the substrates were added. Quenching with water gave a moderate yield and much starting material remained (entry 4). NH_4Cl led to low conversion and no amide was formed (entry 5). Instead, some imine ($PhCH_2CH{=}NBn$) was formed in trace amounts under these conditions. Using $NaHCO_3$ for quenching, gave a higher yield, but also some side-reactions (entry 6). Finally, we tried to prepare the Ru-NHC complex by ligand transfer from a Ag-NHC-complex, thus avoiding the use of a base altogether (entry 7). However, none of the desired product was observed. This could support the hypothesis that the base serves other roles than to generate the free carbene.

Control experiments were performed to ensure that all the components were required for the reaction to take place. Leaving out either ruthenium or the NHC source did not lead to the desired product. In absence of the phosphine ligand only small amounts of the amide were formed (14 % GC-yield).

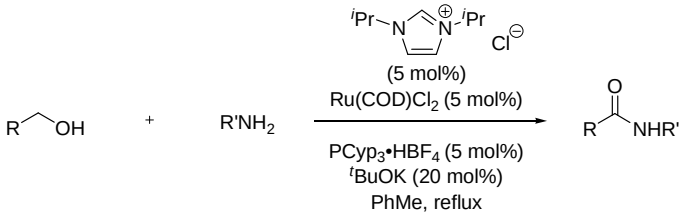
Previously, we had observed that the anion from the imidazolium salt did not influence the outcome of the reaction. However, the influence of the chloride from the ruthenium source had not been examined. Two reactions were carried out where either $AgBF_4$ or

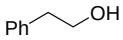
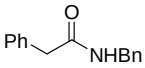
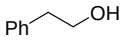
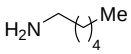
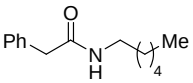
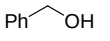
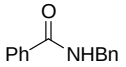
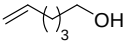
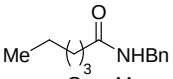
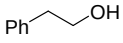
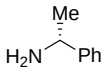
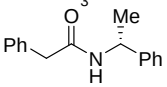
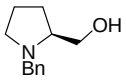
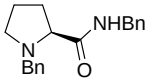
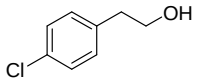
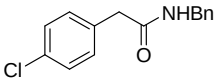
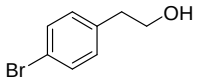
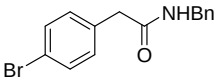
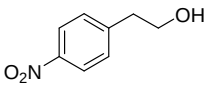
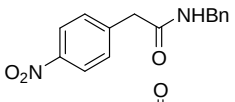
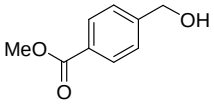
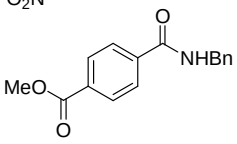
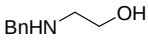
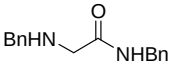
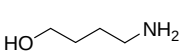
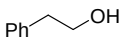
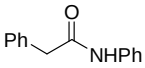
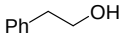
$NaBAr_F$ had been added to exchange chloride for a weakly coordinating anion. In both cases the conversion dropped drastically, and none of the expected product was observed, indicating that the nature of the counter ion is very important for the reaction.

Up to this point all reactions had been performed with a catalyst loading of 5 mol%. We found that for the model reaction 2 mol% gave the same isolated yield after 20 hours. Lower catalyst loadings resulted in incomplete conversion and longer reaction times did not improve the yield.

3.2.3 Substrate scope

At this point we set out to determine the substrate scope for the reaction (table 12). Combinations of simple alkyl and benzyl alcohols and amines gave good to excellent yields (entries 1–3). When an olefin was present the amidation proceeded, but the olefin was reduced in the process (entry 4). A sterically more hindered and optically pure amine also gave the desired amide and no sign of racemization was observed by comparison of the optical rotation of the product to literature values (entry 5; see experimental section for details). To our delight, it was possible to prepare an amide with a chiral center in the α-position without any sign of racemization (entry 6). An aryl chloride performed well (83 % yield; 2 mol% catalyst) in the reaction (entry 7), but the aryl bromide analogue only gave 3 % yield (along with 10 % of the corresponding amine; entry 8). The substrate carrying a nitro group in the same position also resulted in a very low yield (entry 9). The presence of an ester group also had a negative effect in the reaction (entry 10). At 110 °C practically no conversion was observed, but increasing the temperature to 140 °C (in xylenes) did give the desired product in 22 % yield. 10 % of the alcohol was recovered, but the rest had reacted in side reactions. By reacting *N*-benzylethanolamine with benzylamine, we showed that a primary amine can be coupled in good yield in the presence of a secondary amine (entry 11). The amidation reaction could also be performed in an intramolecular fashion to generate a lactam (entry 12). Both aniline (entry 13) and a secondary amine (entry 14) did not undergo reaction under standard conditions, but increasing to the temperature to 163 °C (in mesitylene) led to formation of the desired products, albeit in low to moderate yield.



Entry	Alcohol	Amine	Product	Isolated yield
1				93 %[a]
2				quant.[a]
3				78 %
4				60 %
5				70 %[b]
6				60 %[b]
7				83 %[a]
8				3 %[c]
9				4 %
10				22 %[d,e]
11				90 %
12				65 %
13				21 %[f]
14				40 %[f]

a: 2 mol% Ru, NHC, and phosphine; 8 mol% base. *b*: No racemization had occured.
c: 10 mol% of the corresponding amine was also isolated. *d*: In xylenes at 140 ºC.
e: 10 % alcohol was recovered. *f*: In mesitylene at 163 ºC.

Table 12: Substrate scope of the amidation reaction.

More substrates were tested (figure 9), but most of these resulted in no conversion.[i] In some cases traces of the amide product were observed by ^{1}H NMR, but the products could not be isolated.

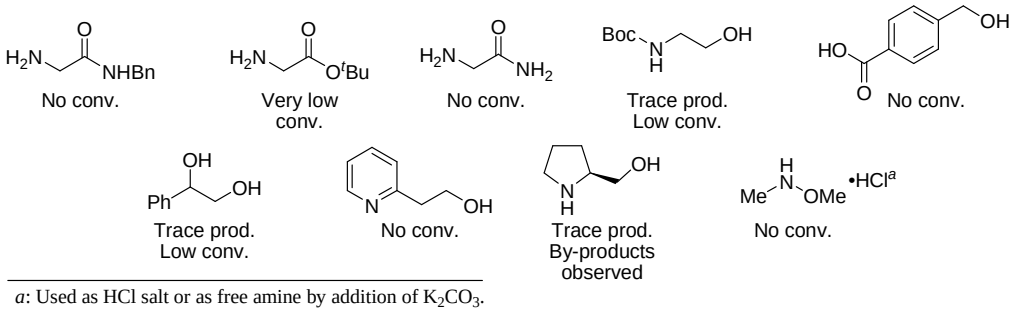
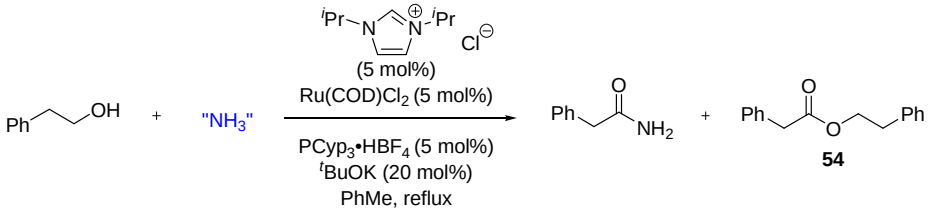


Figure 9: Substrates that did not lead to formation of the corresponding amide.

Most of the substrates that did not react have two (or more) Lewis basic heteroatoms in close proximity. Therefore these could potentially bind strongly to the metal center, thereby inactivating the catalyst.

Next, we examined the possibility to synthesize primary amides from ammonia (or ammonia equivalents). In neither case was the primary amide observed, but in a number of cases the ester **54** was formed in high yield (table 13).



Entry	Ammonia source	Result
1	24 % aq. NH_3	Incomplete conv. Trace **54**
2	$NH_{3\ (g)}$ in PhMe	No conv.
3	$LiNH_2$	Complex mix.
4	NH_4HCO_3	70 % **54**
5	$Cu(NH_3)_4SO_4•H_2O$	30 % **54**
6	$Mg(NH_3)_6Cl_2$	Low conv. Trace **54**
7	Mg_3N_2	quant. yield **54**
8	NH_2	5-10 % **54**
9	H_2N-OH[a]	No conv.

a: Used as both HCl salt or as free amine.

Table 13: The ester 54 was generally the major product when ammonia equivalents were used.

[i] $BnNH_2$ or 2-phenylethanol was used as the other substrate.

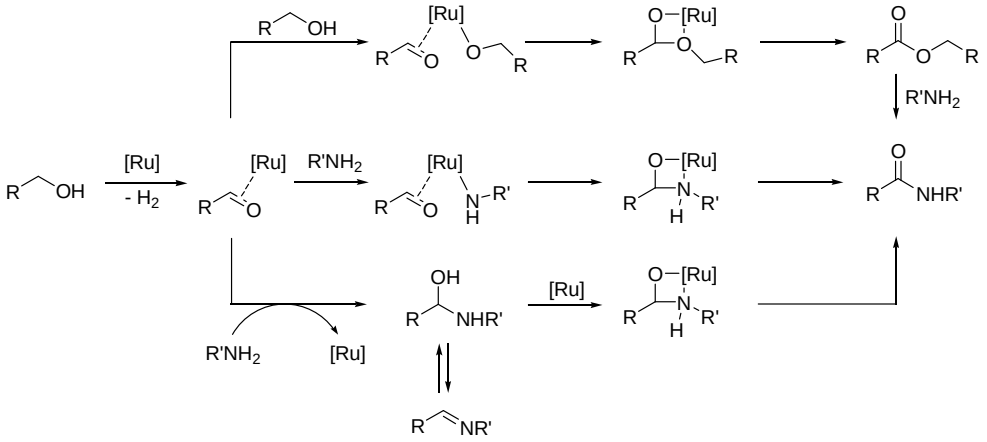
Aqueous ammonia resulted in the formation of a number of different compounds, none of which was the amide (entry 1). Instead, the ester **54** was formed in low yield. A saturated solution of ammonia in toluene did not give any conversion (entry 2), probably due to the low solubility of ammonia at high temperature. Lithium amide gave a complex mixture with some unreacted alcohol (entry 3). Several salts that are known to slowly release ammonia were then used (entries 4–7) and various degrees of conversion were observed. The product was, in all cases, the ester **54**. With magnesium nitride the yield of **54** was quantitative. Allylamine was used since *N*-allyl amide can be isomerized by ruthenium and then give de-allylated products after hydrolysis.[85] Once again the desired amide (or allylated intermediate) was not observed. Only a small amount of **54** had been formed. Finally, we tested if hydroxylamine could lead to the amide via a metal catalyzed Beckmann rearrangement.[39] In this case no conversion of the alcohol was observed.

Since **54** was formed efficiently in the presence of ammonium bicarbonate or magnesium nitride, we speculated if these salts could have an activating effect on the catalytic system. However, when either of the two salts was added to the reaction between 2-phenylethanol and $BnNH_2$, a mixture of the amide and **54** was obtained.

The standard reaction between 2-phenylethanol and $BnNH_2$ in presence of the *in situ* generated catalyst was also tried with three different coupling reagents: pentafluorophenol, DMAP, and HOBt hydrate. In all three cases the yield was significantly lower than without any additive.

3.2.4 Mechanistic studies

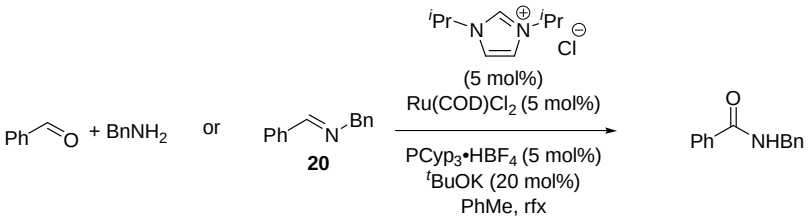
One can envision the amidation reaction to proceed via different routes. Most likely the alcohol is initially oxidized to the aldehyde. One possibility is then the formation of an ester (like **54**) which can react with the amine in a subsequent reaction (scheme 38, top). Alternatively, the amine can add to the aldehyde to give a hemiaminal, which can then undergo oxidation to the amide. Hemiaminal formation can potentially take place in solution (scheme 38, bottom) or in the coordination sphere of the metal (scheme 38, middle). Since the structure of the catalyst is not known the oxidation state and ligands such as hydrides have been omitted in scheme 38.



Scheme 38: Possible pathways from the alcohol to the amide.

The conceivable intermediates (imine and ester) have at no time been observed by GC (except trace amounts when an acid was added to quench the excess base; see table 11), which may indicate that the middle pathway in scheme 38 is the correct one. However, we wanted to verify this by subjecting the intermediates to the reaction conditions. First, the ester **54** was prepared by acylation, and then added to refluxing toluene containing the preformed catalyst and benzylamine. We found that **54** is stable to these conditions and concluded that the amidation reaction does not proceed via the ester intermediate.

Next, we investigated if the aldehyde is released into the solution before further oxidation. If this was the case an imine would be formed transiently. Benzaldehyde or the corresponding imine **20** was reacted with the preformed catalyst under different conditions (table 14).

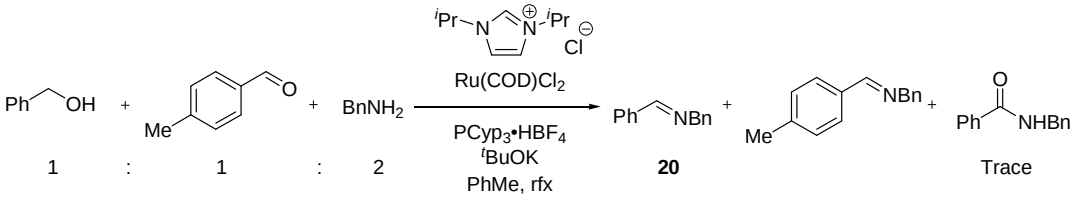


Entry	Substrates	Comment	Result
1	$BnCHO + BnNH_2$	-	**20** quant. yield
2	**20**	-	No conv. of **20**
3	**20**	1 equiv. H_2O added	No conv. of **20**
4	**20**	Under H_2 atmosphere	No conv. of **20**
5	$C_6H_{13}CHO + BnNH_2$	-	Imine formed

Table 14: Imine 20 was unreactive under the reaction conditions.

When benzaldehyde and benzylamine were added to the catalyst the imine **20** formed rapidly and did not react any further (entry 1). The same result was observed when heptanal was used instead of benzaldehyde (entry 5). Preformed **20** was also reacted with the catalyst alone (entry 2), in the presence of water (entry 3) or under a hydrogen atmosphere (entry 4). In all cases no conversion of the imine was observed. These results support the hypothesis that the substrate is not released from the catalyst at the aldehyde stage.

Competition experiments between an aldehyde and an alcohol (scheme 39) resulted in the expected formation of the imine from the aldehyde substrate.[j] We also observed that the alcohol substrate was only transformed into the amide in trace amounts.



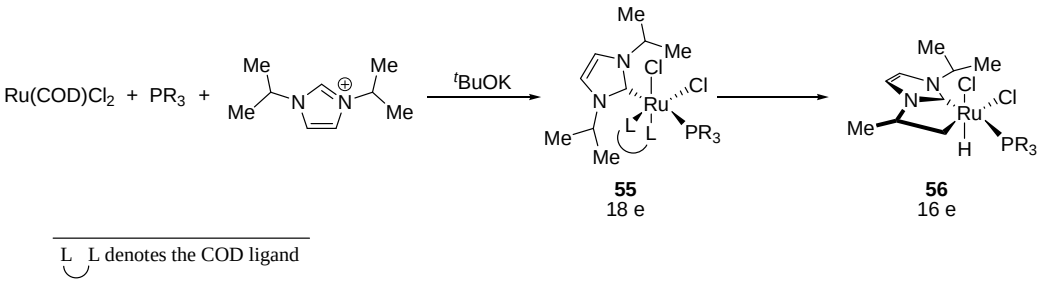
Scheme 39: The amide was only formed in trace amounts in the presence of an imine.

Small amounts of the alcohol remained and the rest had also been turned into the imine. Not only does the imine not enter the catalytic cycle, it also interferes with other reactants. This was also shown by adding imine **20** two hours into a reaction between benzyl alcohol and benzylamine. After addition of the imine the conversion of the alcohol into the amide was slowed significantly, but not suppressed completely. The imine can probably coordinate strongly to the metal and thereby prevent the substrates from reacting effectively. It is interesting, however, to note that significant amounts of the alcohol was oxidized to the aldehyde stage, but only trace amounts was converted to the amide. This indicates that the imine can displace the aldehyde from the metal center, but not the alcohol. Even small amounts (2–5 mol%) of an imine was enough to effectively inhibit the amidation reaction. If the substrate was released from the catalyst during the course of the reaction (scheme 38, bottom) this would result in imine formation and this in turn would inevitably lead to a self-inhibition of the amidation reaction. Therefore we can conclude that the entire reaction must take place on the metal (scheme 38, middle).

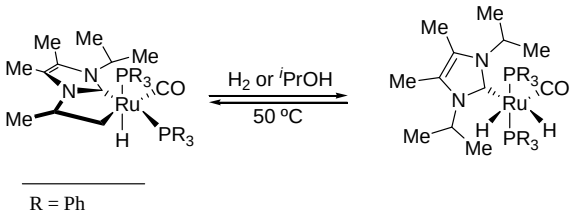
[j] When the substrates were used in a 1:1:1 ratio only imine and alcohol were observed.

The evolution of hydrogen-gas was measured by connecting the reaction vessel to a burette with a water reservoir. The reaction was performed on a 2 mmol scale (2.5 mol% catalyst loading) and after 20 hours 70 mL of gas had evolved. Using the ideal gas law[k] the yield was calculated to be 73 %, and the GC-yield was 86 %. With this result it was concluded that hydrogen-gas is indeed the by-product from the amidation reaction.

As was mentioned earlier, it was not possible to isolate any well defined ruthenium complex, and consequently the structure of the catalytically active complex is not known. From the stoichiometry the 18 electron complex **55** seems likely (scheme 40).[l] However, related complexes are known to undergo C-H activation and form cyclic structures like **56**.[84] Similar Ru-complexes can readily participate in oxidation of *e.g.* alcohols (scheme 41), and therefore a cyclic complex resembling **56** could indeed be the active catalyst.



Scheme 40: Proposed structures of the *in situ* formed Ru-complexes.

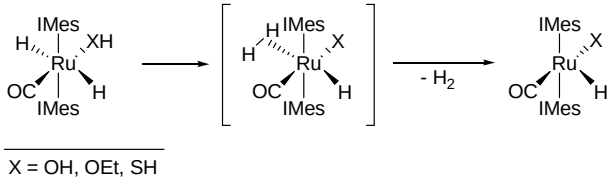


Scheme 41: C-H activated Ru-NHC complexes can oxidize alcohols. Taken from ref. 84e.

It should also be noted that a more straightforward oxidation mechanism that does not involve C-H activation has been shown by DFT studies to be reasonable (scheme 41).[86] In this case a β-hydride elimination of the alcohol (XH in scheme 42) could lead to the corresponding aldehyde coordinated to the resulting Ru-H complex.

[k] At 21 °C and 1 atmosphere pressure

[l] The ligands have been arranged arbitrarily around the metal.



Scheme 42: Alternative mechanism for H_2 release from a Ru-NHC complex. Taken from ref. 86.

3.2.5 Future studies

The results obtained thus far have been accepted for publication in *Journal of the American Chemical Society*, and the project will be continued in the Madsen group. The first goal will be to identify the structure of the catalytically active ruthenium complex. This will possibly allow more effective methods for the catalyst preparation, and lower catalyst loadings can then be realized. More importantly, determination of the structure along with mechanistic studies will provide the insight needed to rationally design improved catalysts with better activity and substrate tolerance.

3.3 Conclusion

A new catalyst was discovered for the direct amide formation from alcohols and amines. The reaction does not require a stoichiometric oxidant and hydrogen gas is the only by-product. This renders the reaction highly efficient from an atom-economy point of view.

The catalyst system was optimized with respect to the phosphine and NHC ligands. The examination of the substrate scope showed that the reaction gives good to excellent yields for unhindered alkyl- and benzyl-amines and -alcohols. Asymmetric centers are tolerated (even in the α-position). Unfortunately, the reaction is not compatible with several functional groups such as aryl bromides, *N*-Boc, nitro, and ester groups. Finally, we showed that the mechanism does not involve an ester intermediate, but most likely proceeds through a hemiaminal, and that the substrate remains coordinated to the metal center throughout the entire catalytic cycle.

4 Studies Toward the Development of a Diastereo- and Enantioselective SOMO Allylation with 1,2-Disubstituted Allylsilanes

4.1 Introduction

The area of organocatalysis has received enormous attention over the last decade.[87] Before the year 2000 organocatalysis was limited to reactions such as Corey-Bakshi-Shibata (CBS) reduction[88] and Shi epoxidation.[89] The change was primarily brought about by the introduction of chiral secondary amines capable of catalyzing a wide range of reactions. This concept builds on the Hajos-Parrish reaction (also known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction) which is an intramolecular, asymmetric aldol reaction catalyzed by proline.[90] A range of naturally occurring amines *e.g.* proline[91] and cinchona alkaloids[92] (*e.g.* quinine) are widely used as organocatalysts, and derivatives of amino acids such as MacMillan's and Jørgensen's catalysts have proven to be very useful organocatalysts (figure 10).

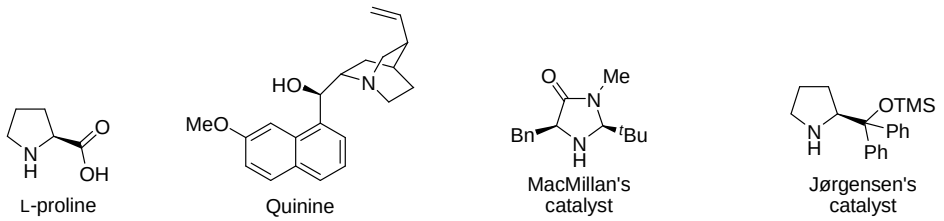
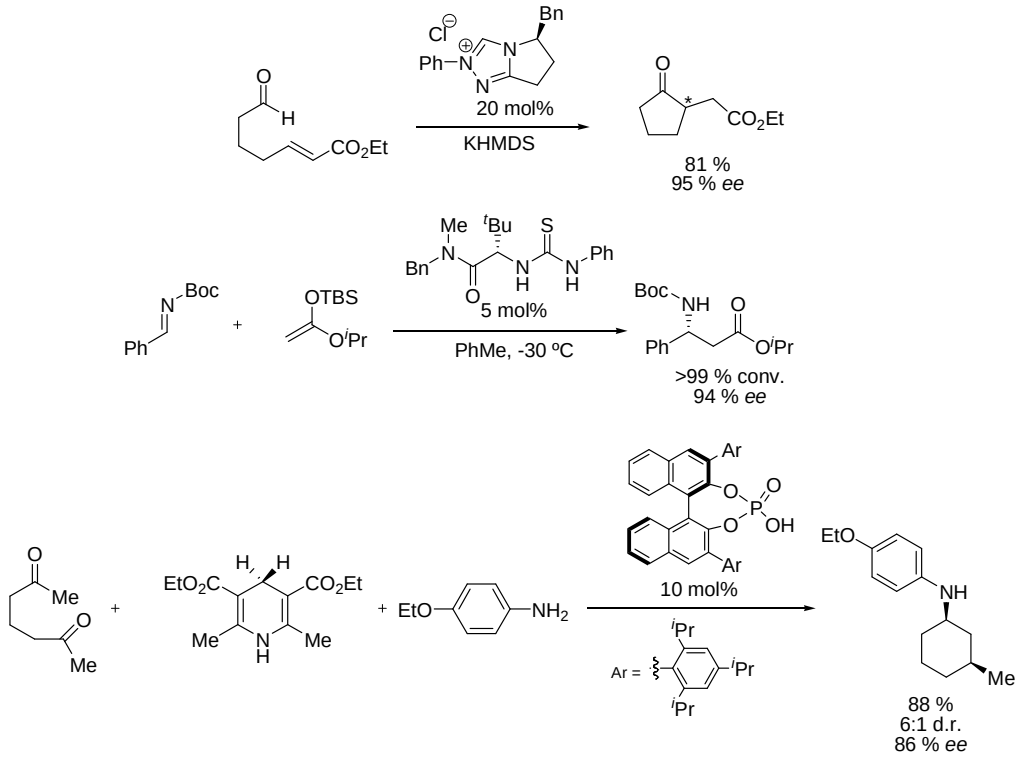


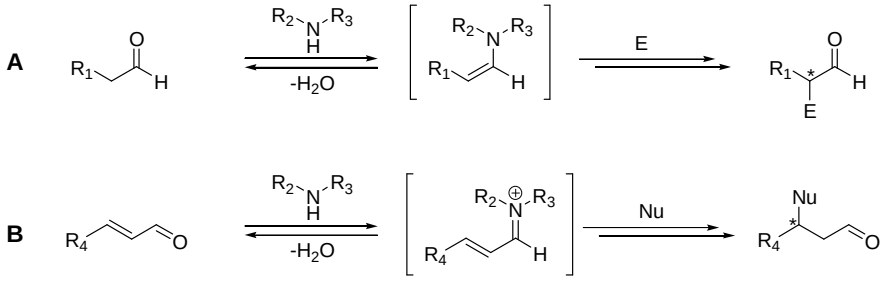
Figure 10: Some common organocatalysts.

Other notable contributions to organocatalysis include carbene catalysts and hydrogen-bonding catalysts. Carbene catalysis has been pioneered by *e.g.* Enders,[93] Rovis,[94] Bode,[95] and Scheidt.[96] The most famous hydrogen-bonding catalysts[97] are based on thiourea,[98] TADDOL,[99] and phosphoric acid[100] scaffolds. The utility of these reactions is illustrated by some examples in scheme 43.



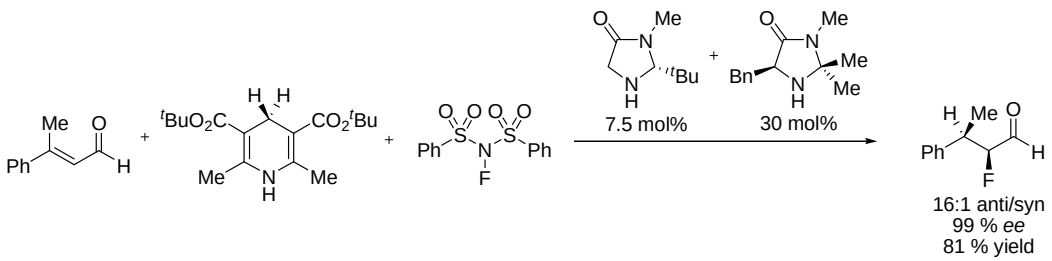
Scheme 43: Examples of organocatalysis by carbene (top) and hydrogen-bonding catalysts (middle and bottom). Reproduced from refs. 93, 98b, and 100.

Most organocatalytic reactions utilizing secondary amine catalysts generate one of two reactive intermediates: either an enamine or an iminium ion. The enamine reacts as a nucleophile (scheme 44A) and the iminium ion as an electrophile (scheme 44B).



Scheme 44: General reaction pathways for enamine (A) and iminium (B) catalysis.

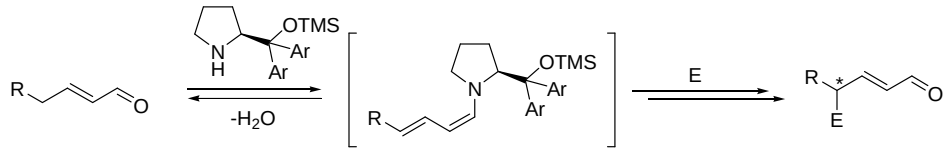
The activation modes are known as HOMO activation (enamine catalysis) and LUMO activation (iminium catalysis). MacMillan has shown that the two activation modes can be elegantly combined in a cascade reaction that adds both a nucleophile and an electrophile to an α,β-unsaturated aldehyde (scheme 45).[101]



Scheme 45: A cascade reaction combining both iminium and enamine catalysis.

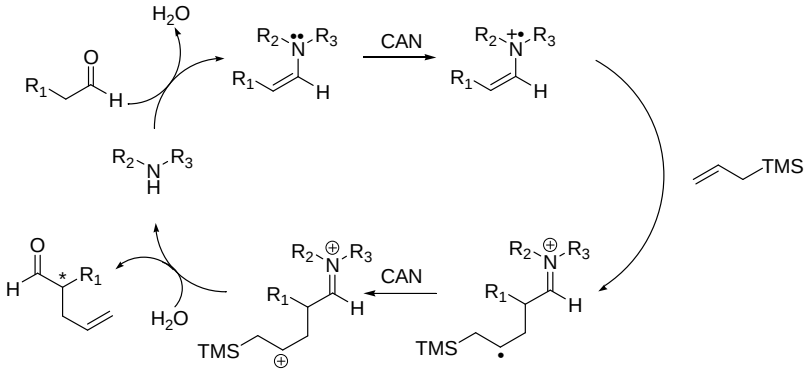
By varying the combination of the catalysts all four stereoisomers of the product are available.

Recently, Jørgensen and co-workers extended the enamine concept by introducing a dienamine activation strategy (scheme 46).[102]



Scheme 46: Dieneamine catalysis developed by Jørgensen.

The latest activation mode was developed by MacMillan and co-workers and dubbed SOMO activation.[103] This activation mode requires a single electron oxidant (such as ceric ammonium nitrate, CAN) that will react with an enamine and generate a radical cation that will react with a suitable "SOMO-phile" (scheme 47).

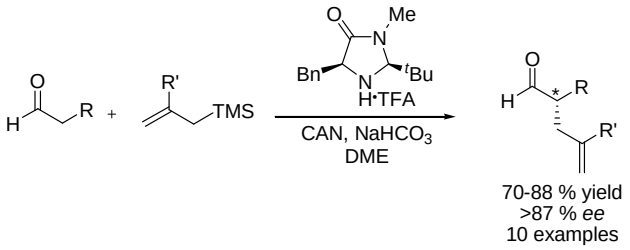


Scheme 47: Proposed mechanism for the organocatalytic SOMO-allylation.

The SOMO-philes can be allylsilanes, heterocycles,[103] enolsilanes,[104] and vinyl potassium trifluoroborate salts.[105]

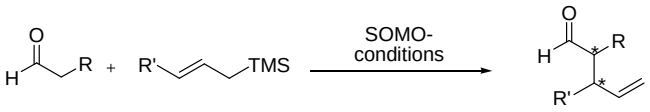
4.2 Aim of the project

Previous work in the MacMillan group had established that the allylation of aldehydes with allylsilanes can be performed using SOMO-conditions. The allylation works well with mono- or 1,1-disubstituted allylsilanes in a process that generates one new stereogenic center (scheme 48).[103]



Scheme 48: Previous results of SOMO-allylation of aldehydes.

In the present project the goal was to expand the scope to 1,2-disubstituted allylsilanes and thereby creating two new three-carbon stereocenters (scheme 49).



Scheme 49: Aim of the project: allylation with 1,2-disubstituted allylsilanes.

After optimization of the conditions, the scope with respect to the R and R' substituents would be examined. The effect of the olefin geometry of the substrate on the outcome of the reaction would also be tested.

4.3 Results

4.3.1 Substrate synthesis

For optimization studies it was decided that an aldehyde and an allylsilane with simple alkyl substituents would be preferable substrates for the model reaction. Octanal was chosen as the aldehyde, and the *n*-hexyl substituted allylsilanes **57** and **58** (figure 11) were found to be better suited than their lower homologous due to their lower volatility.

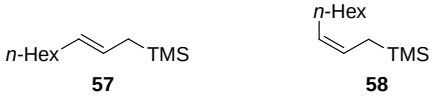
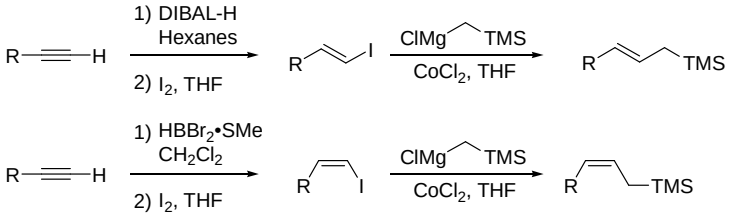


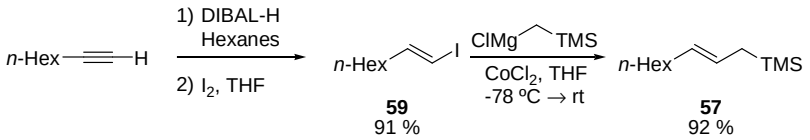
Figure 11: Allylsilane substrates for optimization studies.

For the synthesis of **57** and **58** different synthetic routes were considered. Cross metathesis was rejected due to the poor *E*:*Z* selectivity (typically 2:1 to 5:1) that would be expected from such a reaction.[106] Furthermore, this would only be useful for the preparation of the *E*-isomer. A more effective synthesis of both *E*- and *Z*-allylsilanes was devised based on work by Knochel[107] and Oshima.[108] Starting from 1-octyne Knochel and co-workers used DIBAL-H and $HBBr_2 \cdot SMe_2$ to synthesize *E*- and *Z*-vinyl iodides, respectively. Using the cobalt catalyzed Kumada coupling described by Oshima and co-workers, the allylsilanes should be obtained in good isomeric purity (scheme 50).



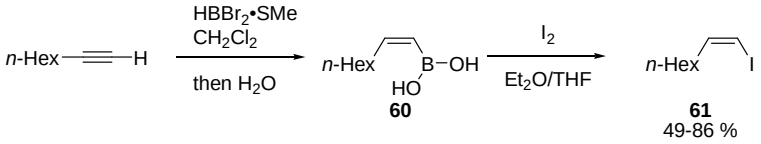
Scheme 50: Synthetic routes to both *E*- and *Z*- allylsilanes.

The DIBAL-H reduction followed by quenching with iodine gave the vinyl iodide (**59**) in good purity (the *Z*-isomer was not detected by NMR), and acceptable yield (76 %). In later experiments it was observed that a higher yield (up to 91 %) could be achieved by not removing the hexanes before the addition of THF and iodine. The Kumada coupling was then carried out, but the selectivity was found to be much lower than described by Oshima and co-workers. A palladium catalyzed Negishi coupling[109] and a Co(III) catalyzed Kumada coupling[110] were then attempted, but neither of these gave the desired product in useful yields. Oshima's method was then reexamined, and it was found that addition of the Grignard reagent at -78 °C instead of 0 °C gave **57** with an *E*/*Z* ratio of >99:1 (by GC) and in a yield of 92 % (scheme 51).



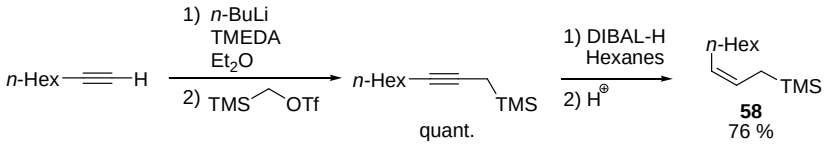
Scheme 51: Synthsis of allylsilane 57 (*E*/*Z* > 99:1).

The synthesis of **58** started from 1-octyne but this time $HBBr_2 \cdot SMe_2$ was used as the reducing agent (scheme 52).



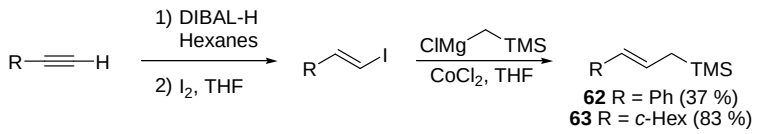
Scheme 52: Synthesis of *Z*-vinyl iodide.

The boronic acid intermediate **60** was transformed into the vinyl iodide **61** without purification. The iodination product **61** was obtained in poor overall yield (49 %) and the *E*/*Z* ratio was found to be 1:46 (by NMR integration). In a second attempt the yield was increased to 86 %, but the *E/Z* ratio dropped to 1:32. Because these levels of isomeric purity were not ideal for evaluating the SOMO reaction another route was chosen. Since it had previously been observed that alkyne reduction with DIBAL-H gave excellent isomeric purity, it was decided to utilize this strategy once more, in this case after introduction of the silane. (scheme 53). 1-Octyne was first alkylated[111] (quantitative yield) and the triple bond was then reduced to give **58** in good yield (76 %). As expected, excellent isomeric purity of the product was observed (*Z/E* >99:1).



Scheme 53: Synthesis of allylsilane 58.

With these useful synthetic routes in hand the phenyl and cyclohexyl substituted allylsilanes **62** and **63** were synthesized (scheme 54) in 37 % and 83 % overall yield, respectively. The low yield in the case of **62** can be explained by the instability of the vinyl iodide intermediate.



Scheme 54: Synthesis of phenyl and cyclohexyl substituted allylsilanes 62 and 63.

At a later stage in the project a methyl substituted allylsilane was needed, and due to the volatility of compound **64** an allylsilane with a heavier silyl group was found to be favorable (**65**; figure 12).

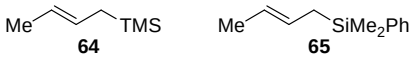
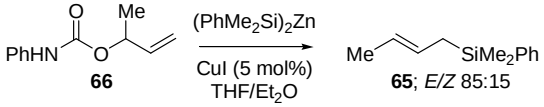


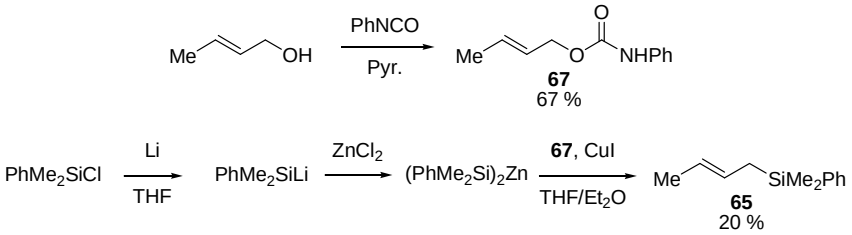
Figure 12: Allylsilane 66 was used instead of 65 because of volatility issues.

The synthesis of **65** has been reported by Oestreich and Auer.[112] The reported synthesis used carbamate **66** as substrate in a copper catalyzed displacement reaction (scheme 55). However, this $S_N2´$ displacement was found to be non-selective and gave rise to a mixture of isomers.



Scheme 55: Oestreich and Auer's synthesis of 65.

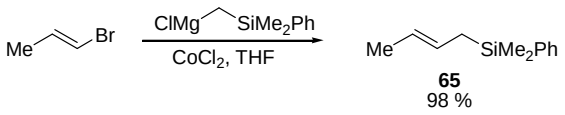
Exposing carbamate **67** to the same conditions should generate **65** in good isomeric purity, since the direct S_N2 displacement was reported to be more selective than the $S_N2´$. The carbamate was synthesized from crotyl alcohol and phenyl isocyanate in 67 % yield (scheme 56) and was then treated with the *in situ* generated zinc reagent to give **65** in 20 % yield.



Scheme 56: Formation of 65 by a Cu-catalyzed displacement reaction.

The reaction was carried out twice but in both cases the yield was around 20 %. It was then decided to try the Kumada coupling for this synthesis. Vinyl bromides are known to react more slowly in the Kumada coupling, but because the vinyl iodide was not commercially available the vinyl bromide was tested. The reaction was, however, found

to work very well with the vinyl bromide and freshly prepared Grignard reagent (scheme 57).

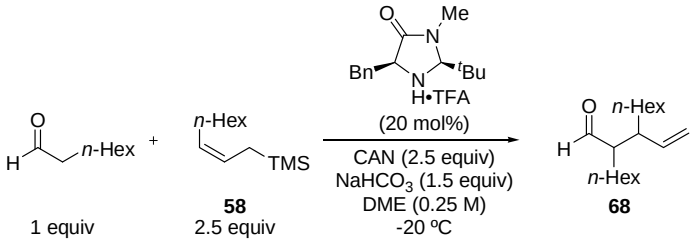


Scheme 57: Synthesis of 65 by Kumada coupling.

With 3 equivalents of the Grignard reagent the yield was almost quantitative, while using 2 equivalents reduced the yield to 86 %. In both cases only the *E*-isomer was observed by NMR.

4.3.2 SOMO allylation of aldehydes

Initially the organocatalytic allylation was carried out with **58** and octanal under the conditions that had been found to be optimal for the allylation with less substituted allylsilanes (scheme 58).[103]



Scheme 58: Initial conditions for the SOMO allylation.

It should be noted that the DME was not dried before use, because traces of water are important for the reaction to proceed. ^{1}H NMR analysis of the crude product revealed that the majority of the starting material remained and that the α,β-unsaturated aldehyde **69** (figure 13) was the major product.

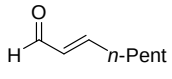
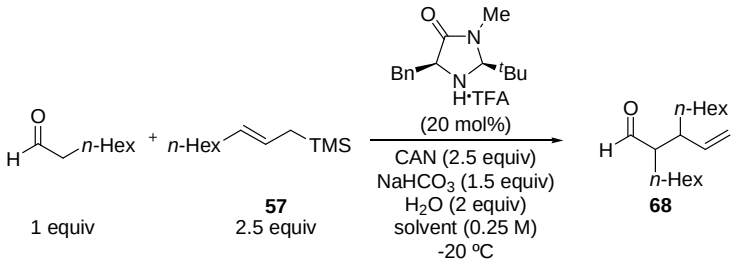


Figure 13: *trans*-2-Octenal (69) was the major product from the attempted allylation reaction.

The ^{1}H NMR spectrum also showed two new peaks in the aldehyde region, but these products could not be isolated. From the crude ^{1}H NMR spectrum is was not possible to conclude if these compounds were diastereomers of the desired product or an unexpected by-product. The reaction was then carried out again with acetone as the solvent. This time the solvent had been dried and 2 equivalents of water were added to the reaction mixture. The result of this reaction was similar to that of the previous reaction in the sense that much starting material remained and that **69** was the major product. Again two new aldehyde peaks were observed, but at slightly different chemical shifts. Unfortunately, these products could not be isolated and characterized. In an attempt to isolate all products, the reaction was carried out a third time, again with DME as solvent, on a larger scale (using 1.3 mmol aldehyde this time instead of the 0.25 mmol that had been used previously). After column chromatography the starting materials were recovered (80 % **58** and 30 % octanal) along with 17 % **69**. No other compounds were isolated. Because considerable amounts of the aldehyde had been consumed, but no product could be isolated, it seemed likely that the allylsilane was not sufficiently reactive under these conditions. Therefore, it was decided to try the reaction with allylsilane **58** (scheme 59) since the difference in olefin geometry could lead to less steric interactions with the radical cation intermediate.

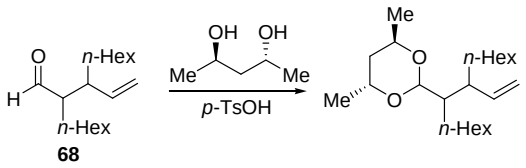


Scheme 59: SOMO allylation with the *E*-allylsilane 57.

Four parallel reactions were carried out with different solvents: DME, acetone, THF, and acetonitrile (no water was added in the reaction using DME). TLC analysis of the reaction mixtures showed a new compound in all four cases with the reaction performed in acetonitrile being the most promising. The product was obtained in 15 % yield and identified as an inseparable mixture of diastereomers of **68** (d.r 1:4 ratio by NMR).[m]

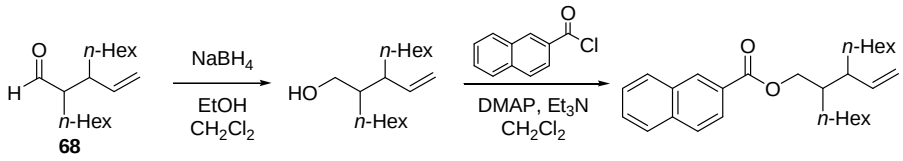
[m] At this point the relative stereochemistry could not be assigned. *Vide infra*.

Unfortunately, GC could not be used to determine the *ee* (or d.r.) of the aldehyde or the corresponding alcohol obtained after $NaBH_4$ reduction. To overcome this problem the four stereoisomers of the aldehyde were converted into 4 diastereomers by acetal formation with either (*S,S*)-2,4-pentanediol or (*R,R*)-2,4-pentanediol (scheme 60), but neither of these could be separated by GC.



Scheme 60: Acetal formation with (*R,R*)-2,4-pentanediol.
The (*S,S*) version was also prepared.

Reduction to the alcohol followed by esterification with 2-naphthoyl chloride (scheme 61) gave UV-active derivatives, and these could be separated by SFC (HPLC was also tried, but was unsuccessful), and the 1:4 d.r. was confirmed and the *ee* of the major diastereoisomer was found to be 94 %.[n]



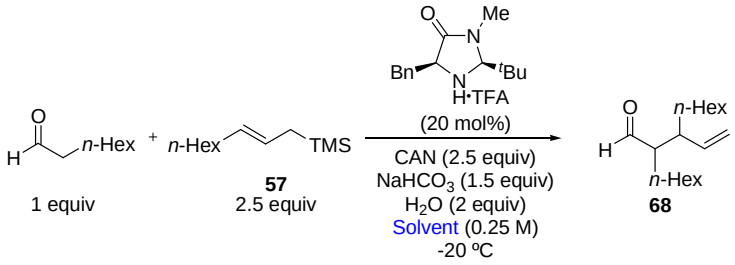
Scheme 61: Synthesis of UV-active derivatives for determination of *ee*.

Reduction of the crude reaction mixture gave rise to a complex mixture with significant loss of product, and consequently column chromatography was necessary at the aldehyde stage before the reduction. After esterification a second chromatographic separation was necessary to remove UV-active by-products which would otherwise interfere with the *ee* measurement. Altogether, this made it tedious to obtain the results of the SOMO-reaction, and we considered using an alternative model reaction that would incorporate a UV-group into the product. This was attempted by using **62** as the allylsilane component or 2-phenylacetaldehyde as the aldehyde component. Both these reactions resulted in complex mixtures from which none of the desired product could be

[n] For the determination of the *ee*, racemic product was obtained by repeating the reaction with a racemic catalyst.

isolated. With these results we decided to continue the screening process with the reaction described in scheme 59.

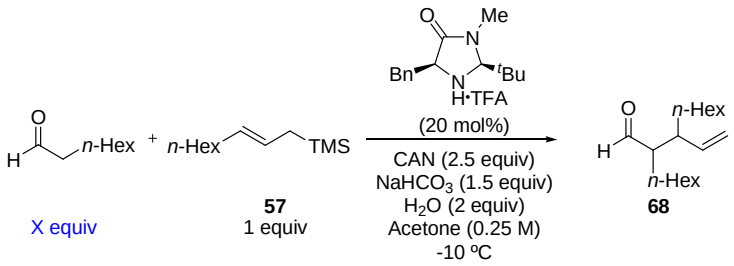
With methods in hand to determine GC-yields, d.r. and *ee*, the screening of the variables could commence. First, the influence of the solvent was examined. DME, THF, acetone, and acetonitrile were tried since these were known in the group to give the best results for similar SOMO-reactions. Toluene was included because its effect on SOMO-reactions was not known at that time. Aside from the solvent all conditions were kept the same as described in scheme 59. The results of the solvent screening are summarized in table 15.



Solvent	GC-yield (%)	d.r.	ee (%)
DME	5	n.d.	n.d.
THF	17	n.d.	n.d.
PhMe	no reaction	-	-
Acetone	48	4:1	94
MeCN	24	3:1	92

Table 15: Solvent screening for the allylation reaction.

From the solvent screening it was obvious that acetone was the superior solvent giving the highest yield, high *ee* and acceptable d.r. The next step was to determine the optimal temperature for the reaction, and the reaction was repeated at -30, -10, and 0 °C with acetone as the solvent. This gave GC-yields of 27, 50, and 29 %, respectively. Up until this point an excess of **57** had been used in the reactions, but since this reagent was more precious than the commercially available octanal it was examined if comparable results could be obtained with **57** as the limiting reagent. The results of these experiments are summarized in table 16.



equiv. octanal	GC-yield (%)
1.0	35
1.5	40
2.0	47
2.5	38
5.0	38

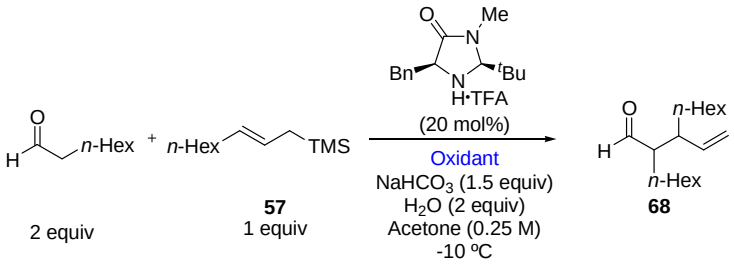
Table 16: Allylation with various amounts of octanal.

Switching from a octanal:**57** ratio of 1:2 to 2:1 gave essentially the same yield. The d.r. was found to be 4:1 and the *ee* was 94 %. Other ratios of substrates gave poorer yields.

The next parameters to be examined were reaction time and concentration. A reaction time of 44 hours (as compared to the 24 hours used previously) led to a decrease in the yield to 35 %. Experiments with reaction times shorter than 24 hours were not carried out since starting material still remained at this time, and product decomposition had not set in. Therefore no improvement in yield would be expected from shorter reaction times. The concentration of the reactants might play an important role. Higher concentration would normally be expected to increase the reaction rate, but due to the limited solubility of CAN at -10 °C it could also be advantageous to increase the volume and thereby increase the availability of the CAN. Increasing the concentration from the usual 0.25 M to 0.50 M led to a decrease in yield to 42 % and a slight decrease in *ee* to 92 %. The d.r. was, however, improved to 5:1. Lowering the concentration to 0.125 M drastically decreased the yield to 18% (d.r. and *ee* were not determined).

The amount of oxidant was then varied (table 17), and another useful single electron oxidant, namely $Fe(phen)_3(PF_6)_3$,[113] was also tried (entry 4). The experiment with the iron complex did not give any of the desired product. The iron complex had been used for

another project in the group and a different stoichiometry had been found to be optimal.[o] The allylation was also carried out with this ratio of reagents (entry 5), but no improvement was observed.



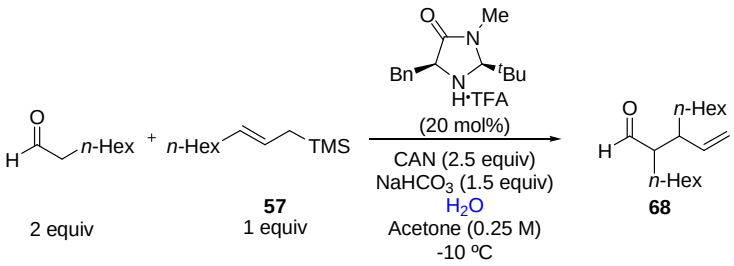
Entry	Oxidant	Equiv of oxidant	Yield (%)
1	CAN	2.0	30
2	CAN	2.5	44
3	CAN	3.0	31
4	$Fe(phen)_3(PF_6)_3$	2.5	0
5	$Fe(phen)_3(PF_6)_3$[a]	3.0	0

a: Different stoichiometry was used. See footnote o.

Table 17: Screening of the amount of oxidant.

The next step was to find the optimal amount of water for the reaction. The results from the water screening are summarized in table 18. The optimum yield was obtained with 2.0 equivalents of water.

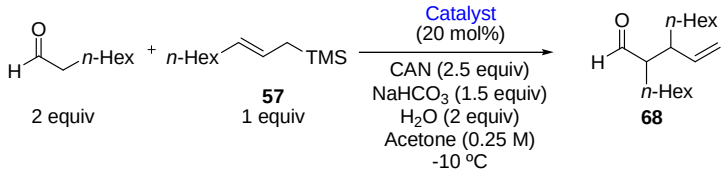
[o] Octanal:**57**:Cat.:$NaHCO_3$:H_2O 3:1:0.2:3:2. Concentration of allylsilane was 0.04 M. Jui, N.; MacMillan, D. W. C. Unpublished results.



Equiv H_2O	GC-Yield	Equiv H_2O	GC-Yield
0.0	25	3.0	24
0.5	28	4.0	32
1.0	32	5.0	26
1.5	33	7.5	22
2.0	51	10	26
2.5	48	15	23

Table 18: Screening for optimal amount of water.

The structure of the catalyst is, of course, also of great importance for the rate and selectivity of the reaction. A thorough catalyst screening was performed with many of the catalysts available in the lab. Some were left out since experience in the group was that they were too unstable to be used under the SOMO conditions. The catalyst screening is summarized in table 19.



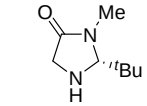
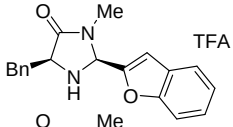
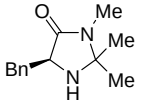
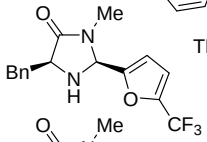
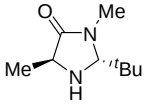
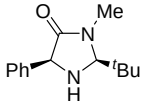
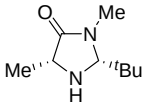
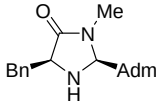
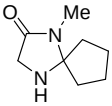
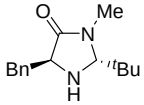
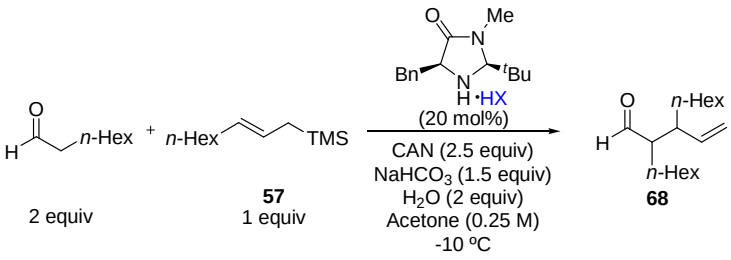
Entry	Catalyst	Co-catalyst	GC-Yield (%)	d.r.	ee (%)	Entry	Catalyst	Co-catalyst	GC-Yield (%)	d.r.	ee (%)
1		TfOH	38	4:1	49	6		TFA	12	n.d.	n.d.
2		TfOH	13	n.d.	n.d.	7		TFA	9	n.d.	n.d.
3		HCl	2	n.d.	n.d.	8		TFA	22	n.d	n.d.
4		TFA	19	n.d.	n.d.	9		TFA	47	4:1	92
5		TFA	14	n.d.	n.d.	10		TFA	7	n.d.	n.d.

Table 19: Results from the catalyst screening.

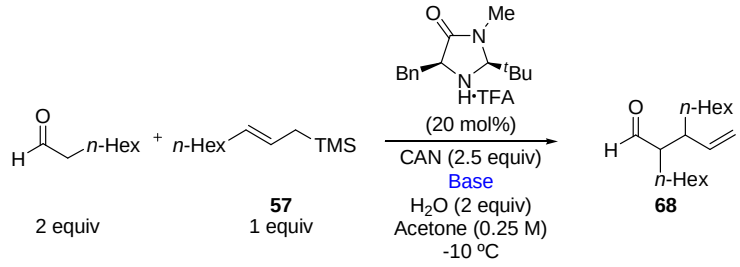
The d.r. and *ee* were only determined in the cases where the GC-yields were comparable to those obtained with the ^{t}Bu,Bn-catalyst used previously. The Adm,Bn (entry 9) catalyst gave essentially the same result as the ^{t}Bu,Bn-catalyst, but all others were inferior. It should be noted that in some cases the catalysts were stored as salts of other acids than TFA and in these cases the catalysts were used directly and not converted to the TFA-salts. It is, however, known that the co-catalyst can have a marked effect on the efficiency of organocatalytic reactions. To examine if this was also the case for this reaction a screening of nine acids was performed. These were chosen, such that a wide pK_a range was covered. As can be seen in table 20 no drastic effect was observed, and a correlation between pK_a and yield was not evident. TFA gave the best result.



HX	pK_a	GC-Yield (%)	HX	pK_a	GC-Yield (%)
none	-	35	TCA	0.51	31
AcOH	4.76	38	TFA	0.23	40
2,4-DNBA	2.81	31	*p*-TsOH	-2.8	37
3,5-DNBA	2.73	39	HCl	-8.0	32
DCA	1.35	35	TfOH	-10	37

Table 20: Screening of the co-catalyst (HX).

The reaction was then carried out with a range of bases that were known to give good results in reactions under similar conditions (table 21).[104] Since $NaHCO_3$ was found to be the best base, the amount of this was also varied.



Base	equiv	Yield (%)	d.r.	ee (%)
None	-	37	4:1	96
$NaHCO_3$	1.5	44	4:1	93
K_2CO_3	1.5	17	4:1	96
DTBP	1.5	14	3.5:1	92
$NaHCO_3$	0.5	22	4:1	n.d.
$NaHCO_3$	1.0	33	4:1	n.d.
$NaHCO_3$	2.0	17	4:1	92
$NaHCO_3$	2.5	16	4:1	94
$NaHCO_3$	3.0	15	4:1	92

DTBP: 2,6-Di-*tert*-butyl pyridine

Table 21: SOMO-allylation with various bases.

Both the absence of a base and the use of a stronger base led to higher levels of enantioselectivity, but diminished yields. The pyridine base also resulted in a much lower yield. The best result was obtained with 1.5 equivalents of $NaHCO_3$, but it had been observed that some results were not consistent. This had also been the case in the water screening, where the experiments had to be carried out several times to give a reliable trend. In the case of the base screening the yields in the reactions with 2–3 equivalents of $NaHCO_3$ were significantly lower than would be expected. In order to avoid these fluctuations, it was decided that a water/base screen should be performed on the automated synthesis equipment available in the MacMillan lab. Initially 16 reactions were run with the amounts of water and $NaHCO_3$ varying over a broad range (table 22).

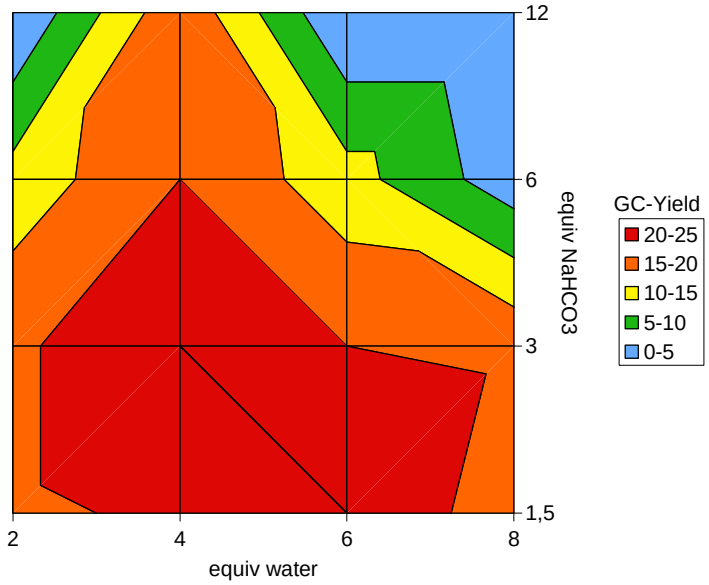


Table 22: Combined water and base screen performed on the synthesis robot.

These experiments showed that the results obtained on the synthesis robot were probably more consistent than when the experiments were carried out manually. One explanation for this could be that the stirring (vortexing) of the heterogeneous reaction mixtures is more uniform on the robot than when many vials were placed in the cryo-cool bath. It is, however, also interesting to notice that the yields obtained this way were significantly lower than the yields obtained previously. This might have been due to less efficient degassing by the synthesis robot. In the next screening the solvent was thoroughly degassed before it was placed in the robot. This screening also included more data points

in a narrower range to give a more precise description of the optimal conditions (table 23).

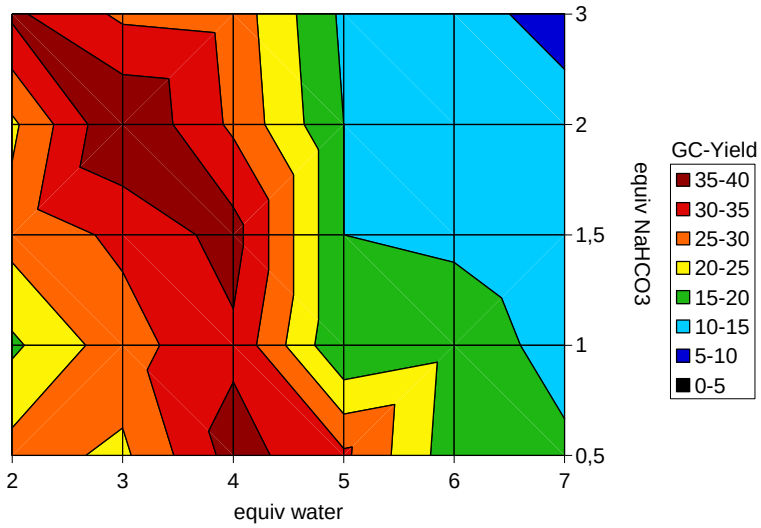


Table 23: Second water/base screen on the automated system.

This time the GC-yields were closer to the results obtained when performing the reactions manually. It is also interesting to note that the optimal conditions identified this way differ somewhat from the optimum identified previously. Even though the optimum was slightly different than the conditions used up to this point, it did not represent a major improvement, and the yield was still too low to be considered useful. The amounts of α,β-unsaturated aldehyde (**69**) formed were also quantified (table 24). The results indicated that the rate of formation for both **68** and **69** are highest at the same concentrations of water and $NaHCO_3$, and therefore **69** is most likely not an inhibitor of the catalyst as could be speculated (*vide infra*).

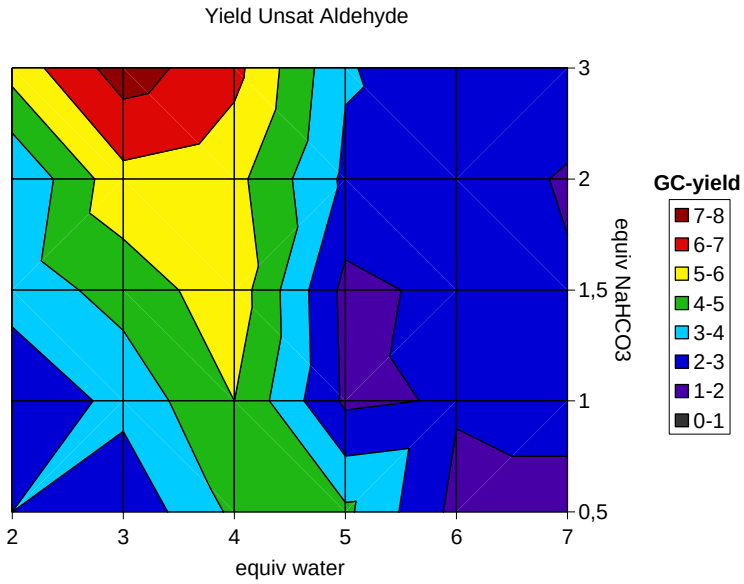
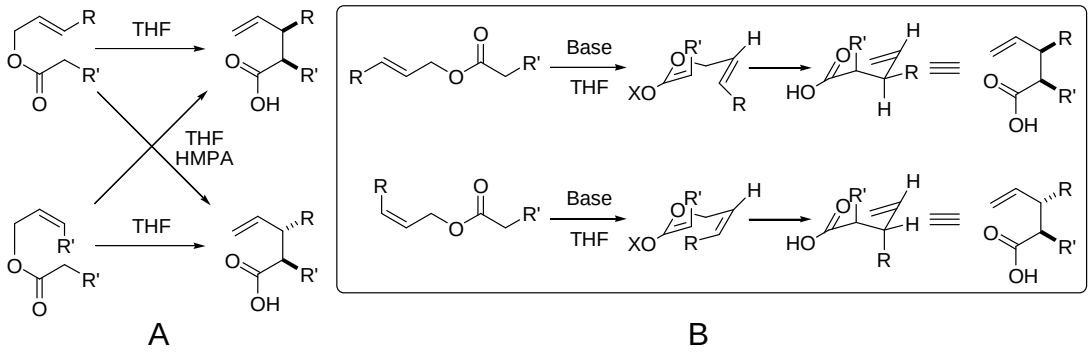


Table 24: Formation of α,β-unsaturated aldehyde 69 as a function of water and base content.

At this point all the variables had been examined and it was not likely that the present system could be optimized to generate better results. The focus of the project was turned toward understanding why the allylation failed to give acceptable yields. First, however, some work was done on assigning the stereochemistry of the allylation products.

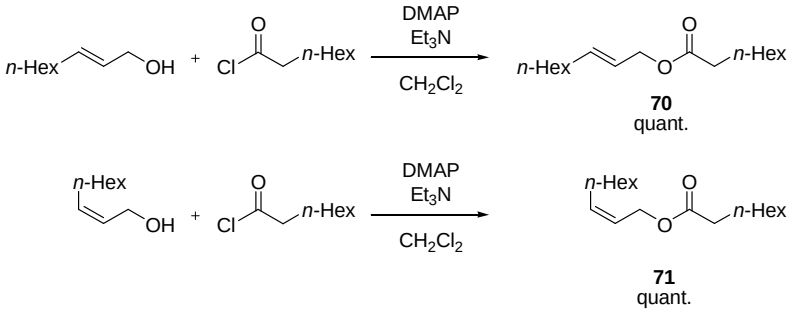
4.3.3 Determination of the stereochemistry

In order to assign the relative stereochemistry of **68**, we planned to compare the spectral data to data of compounds available from a reaction with predicable stereochemical outcome. The Ireland-Claisen rearrangement[114] was found to be well suited for this purpose since the following criteria were met: 1) the Ireland-Claisen product (γ,δ-unsaturated carboxylic acids) and **68** can be easily interconverted, 2) it is known to proceed with high stereoselectivity, and 3) both diastereomers are available through this method. It is known that the stereochemical outcome of the rearrangement is dependent on the olefin geometry of the substrate as well as the choice of solvent and additive (scheme 62).



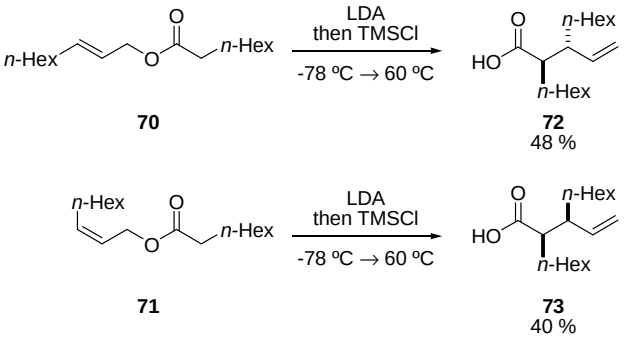
Scheme 62 A: Control of the stereochemistry can be exercised through olefin geometry or choice of solvent. B: Transition state rationale for the outcome (without HMPA). X = anion or TMS.

The (*E*)- and (*Z*)- substrates **70** and **71** were synthesized from octanoyl chloride and (*E*)- and (*Z*)-non-2-en-1-ol, respectively (scheme 63). Both esters were obtained in quantitative yield.



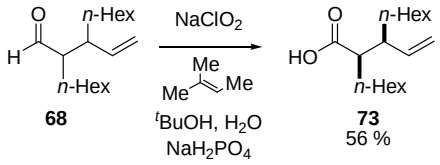
Scheme 63: Synthesis of Ireland-Claisen substrates 71 and 72.

The rearrangement itself was first carried out by adding the ester to LDA in THF at -78 °C and the reaction mixture was then allowed to reach room temperature. However, TLC analysis showed only very little conversion. In a second attempt TMSCl was added 5 minutes after the ester (still at -78 °C) and the reaction mixture was then heated to 60 °C. This time the reaction proceeded more smoothly and the products **72** and **73** were obtained in modest yield (**72**: 48 %; **73**: 40 %) (scheme 64).



Scheme 64: Ireland-Claisen rearrangement.

Pinnick oxidation[115] of **68** led to a compound that was found to be identical to **73** (scheme 65). Thus, the product of the SOMO-allylation (**68**) could be assigned the (2*R**,3*S**) configuration.



Scheme 65: Conversion of the allylation product 68 into the Ireland-Claisen product 73.

This relative stereochemistry and arrangement of functional groups (or closely related groups) is present in two compounds with known absolute stereochemistry and optical rotation, namely 2,3-dimethylpent-4-enoic acid (**74**)[116] and sphaeric acid (**75**)[117] (figure 14).

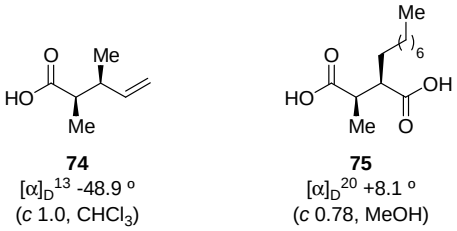
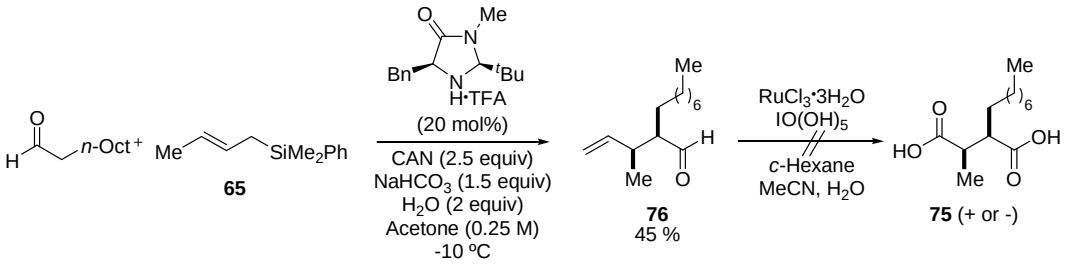


Figure 14: The absolute stereochemistry of 68 could be obtained from comparison with 74 or 75.

To synthesize **74** or **75** (or their enantiomers) by SOMO-allylation an allylsilane such as **65** was required (or alternatively one with an *n*-octyl substituent for sphaeric acid). Since the synthesis of sphaeric acid would constitute a total synthesis of a natural product in just three steps it was attempted first (scheme 66). The SOMO allylation of decanal with

65 proceeded well giving the product (**76**) in 45 % yield (traces of the allylsilane could not be separated from the product). Disappointingly, the final oxidation of the aldehyde and the alkene using Griffith's modification[118] of Sharpless' $RuCl_3/HIO_4$[119] oxidation did not give the desired di-acid.

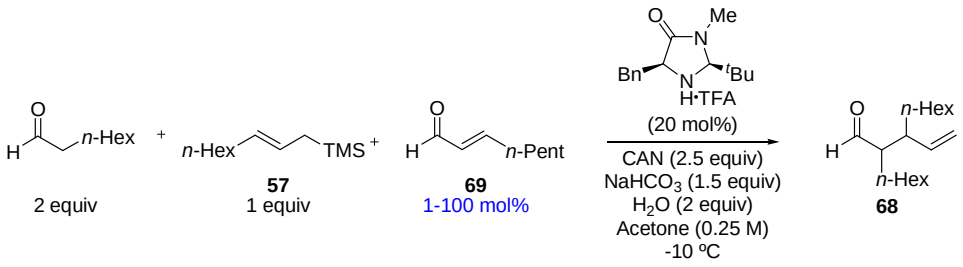


Scheme 66: Attempted synthesis of sphaeric acid.

When these experiments were carried out, the external stay was coming to an end, and it was not possible to repeat them. Oxidative cleavage of the alkene might also be achieved by Lemieux-Johnson oxidation[120] (followed by oxidation of the resulting aldehyde) or ozonolysis.[121] Alternatively, allylation of propionaldehyde with **65** followed by Pinnick oxidation would generate **74** (+ or -) and readily reveal the absolute stereochemistry of the SOMO-product.

4.3.4 Catalyst inactivation

From the results obtained during the screening process it was obvious that the catalyst was inactivated during the reaction. This inactivation seemed to be complete before the catalyst could perform more than 2–3 turnovers. Two working hypotheses were found to be reasonable: 1) α,β-unsaturated aldehyde by-product (**69**) inhibited the catalyst by formation of stable iminium ions, or 2) the catalyst was degraded to a catalytically inactive species. The first possibility was investigated by adding *trans*-2-octenal (**69**) to the SOMO allylation (table 25).

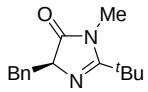


mol% **69**	GC-yield (%)	mol% **69**	GC-yield (%)
1	33	**20**	26
5	29	**100**	20
10	30		

Table 25: Investigation of the possible inhibition of the SOMO allylation by aldehyde 69.

From this inhibition study it was clear that **69** does slow down the reaction somewhat, but this was far from enough to explain the low yields generally observed. The findings that **69** is not an effective inhibitor of the catalyst is also supported by the results in table 24 where the yields of both **68** and **69** show maxima at the same concentrations of water and $NaHCO_3$ (*vide supra*).

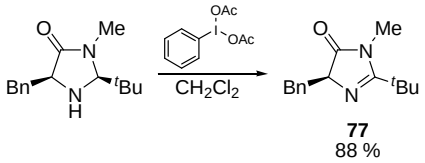
Consequently, the second hypothesis seemed to be the more probable one. It was deemed likely that the catalyst could be oxidized to the amidine **77** (figure 15). This oxidation product has been reported by Lee and MacMillan in the case of epoxidation of α,β-unsaturated aldehydes with hypervalent iodide reagents.[122]



77

Figure 15: Possible product/intermediate in the inactivation of the catalyst.

To test this hypothesis a reference sample of **77** was prepared by Lee and MacMillan's method (scheme 67).



Scheme 67: Synthesis of amidine 77.

The SOMO-allylation was then carried out again with the standard components, once with CAN and once with $Fe(phen)_3(PF_6)_3$ as oxidant. When CAN was used neither catalyst nor **77** was present in the reaction mixture after 24 hours (by TLC analysis). The oxidation product **77** was, however, observed when the iron complex was used as oxidant. These experiments indicate that the catalyst is susceptible to oxidation in the 2-position. In the CAN-case **77** might be an intermediate which could react further by hydration, hydrolysis, or other degradation modes. To further validate this hypothesis some experiments were carried out to detect **77** in the SOMO reaction in the presence of CAN. ReactIR was believed to be a suitable method for this purpose. First the free base of the catalyst was mixed with CAN (2 equivalents) in acetone at room temperature.

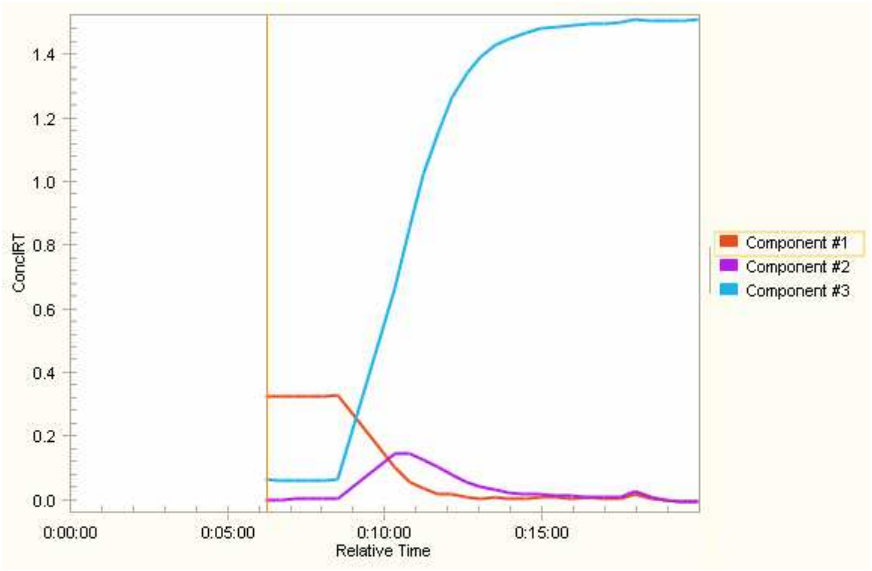


Figure 16: Reaction profile of the reaction with the catalyst (component 1) and CAN (component 3).[p]

Under these conditions the catalyst (figure 16; component 1) was rapidly transformed into a second compound (component 2), which then disappeared within a few minutes

[p] The reaction profile was automatically generated by the ReactIR apparatus based on the intensities of the absorption bands.

(figure 16). Component 3 in figure 16 is most likely CAN slowly coming into solution over several minutes. Component 2 could well be **77** since absorption bands corresponding to this compound were observed in the IR spectrum (figure 17). Unfortunately, the characteristic bands are very close to the bands originating from the catalyst. CAN also has a strong absorbance in this region, and even though some attempts were made to subtract these absorbances, they could not be removed completely. Another uncertainty is the possibility that cerium will coordinate to the catalyst and thereby shift the bands slightly.

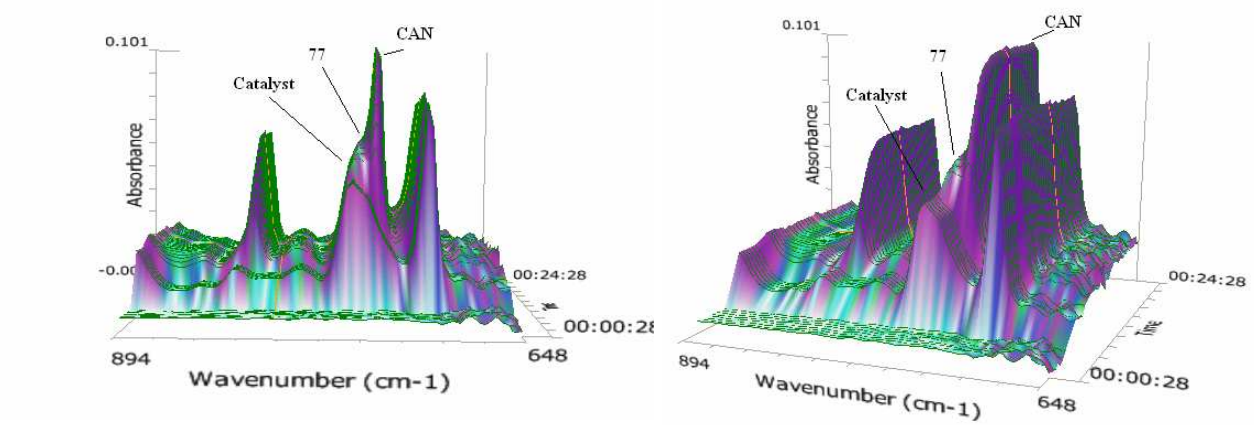


Figure 17: The band at 700 cm^{-1} originates from both the catalyst and 77. The catalyst gives rise to the band at 749 cm^{-1} while the band at 744 cm^{-1} can be attributed to 77.

A similar experiment was carried out at -10 °C and an analogous result was obtained. It should be noted that the reaction setup made it impossible to ensure complete exclusion of air. These results indicate that CAN oxidizes the catalyst rapidly even at -10 °C, and that **77** reacts further under these conditions. However, due to the uncertainties associated with the experimental setup no final conclusion can be made from these indications.

In an attempt to avoid the catalyst degradation in the SOMO reaction, slow addition of a solution of CAN to the reaction mixture was tried. CAN is soluble in several polar solvents, and five of these were used: DMSO,[q] DMF, water, acetone, and MeOH. Surprisingly, only traces of the product were observed in all cases. With methanol the GC-chromatogram showed only little remaining octanal, but one new major peak,

[q] CAN only slightly soluble; slurry was used.

presumably the dimethoxy acetal. In all five cases unreacted allylsilane **57** remained after 24 hours. One explanation for the low conversion could be that the radical cation is formed but since the concentration of CAN was very low the second oxidation event could not take place. This would then force the intermediate to react by some different pathway effectively inactivating the catalyst.

4.3.5 Catalyst design

With the information obtained on catalyst inactivation, it was clear that the key to overcoming the problems would be to develop a novel catalyst. The catalyst used so far had performed the SOMO reaction with a decent reaction rate, acceptable diastereoselectivity and good enantioselectivity. The only draw-back was that it was too prone to oxidation under the reaction conditions. For these reasons continuing with the imidazolidinone skeleton derived from phenylalanine was deemed to be a good starting point for a new catalyst. The hypothesized oxidation of the 2-position can be prevented by two strategies: 1) placing a second substituent in this position, or 2) placing a more electron withdrawing susstituent in the 2-position. The first possibility was rejected because two 2,2-disubstituted catalysts (figure 18A) had already been found to be inferior catalysts for the allylation reaction (table 19, *vide supra*). Two catalysts falling into the second category (figure 18B) had also been tried without success, but it was believed that this scaffold was easier to fine-tune and the steric requirements of the catalyst would not be drastically affected as would be the case for 2,2-disubstituted catalysts.

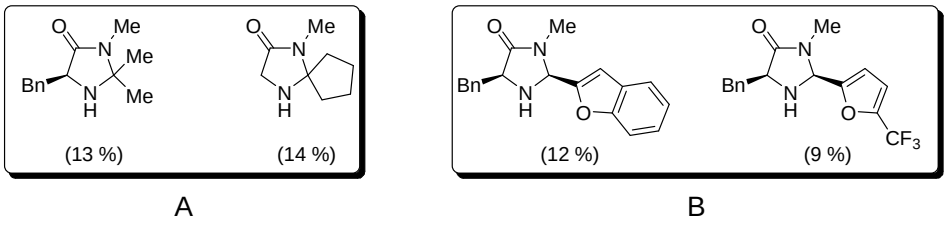
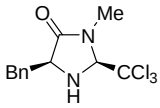


Figure 18: Catalysts made inert to oxidation by disubstitution (A) or electron withdrawing ability of the substituents (B). The previously obtained yields with these catalysts for the standard SOMO allylation are given in parantheses.

For example, replacing the *tert*-butyl group with a trifluoromethyl, trichloromethyl, or $-C(CF_3)_3$ substituent should make the catalyst much more stable toward oxidation in the

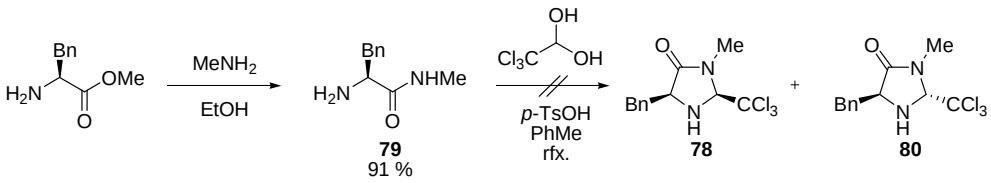
2-position. This stability should of course be weighted against the decreasing nucleophilicity of the amine functionality and ability to form iminium ions and enamines with the carbonyl substrate in a reaction. The trifluoromethyl group was deemed to be too electron withdrawing to make a useful catalyst. The polyfluorinated aldehyde that would be necessary to synthesize the -$C(CF_3)_3$ substituted catalyst was not readily available, and therefore the trichloromethyl catalyst **78** (figure 19) was chosen a as suitable target for catalyst development.



78

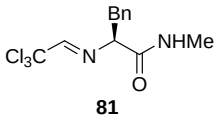
Figure 19: Target for the catalyst development.

The synthesis of **78** started with L-phenylalanine methyl ester which was transformed into the methylamide **79** in 91 % yield (scheme 68).



Scheme 68: Synthesis of intermediate 79 and attempted cyclization to 78 and 80.

The cyclization of **79** to **78** and **80** was attempted with chloral hydrate and a catalytic amount of *p*-TsOH in refluxing toluene. Clean formation of one new product within 30 min. was observed. The reaction was stopped but upon isolation this compound was identified as the imine intermediate **81** (figure 20).

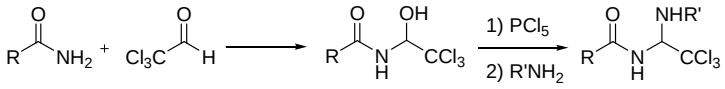


81

Figure 20: Imine 81 was the only observed product for the cyclization.

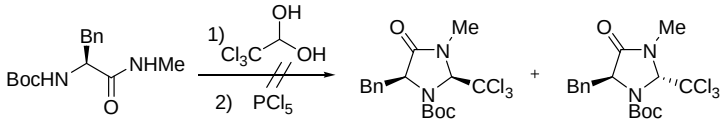
The reaction was then carried out again, and when formation of **81** was observed more *p*-TsOH was added and the reaction mixture was stirred overnight at reflux temperature. TLC analysis of the reaction mixture now showed numerous compounds, none of which

seemed to be present in large quantities. The reaction was then stopped, and the crude product was analyzed by NMR. The spectra were very complex and none of the characteristic signals expected for **78** and **80** were observed. The milder $Yb(OTf)_3$ catalyzed reaction was then tried (THF; rt or 50 °C), but neither heating nor very long reaction times (up to 4 days) led to any significant reaction beyond the imine stage. Related syntheses have been reported[123] by a step-wise manner (scheme 69). First the stable hemiaminal is formed and then chlorinated or dehydrated with PCl_5. This should facilitate the ring closing event.



Scheme 69: Treatment with PCl_5 had been shown to facilitate addition to amid-chloral adducts.

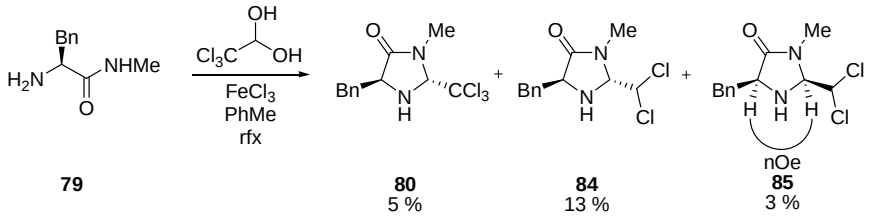
Attempts to synthesize **78** by this route were unsuccessful. The Boc protected amine **82** was also used to ensure that the amide would add to the chloral before the amine. Unfortunately, none of the desired product **83** was observed from this reaction (scheme 70).



82 **83**

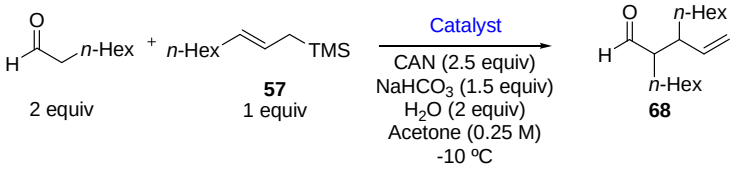
Scheme 70: Attempted ring-closure with the Boc protected amine.

Finally, the Lewis acid catalyzed reaction was tried again, this time with $FeCl_3$ as the catalyst[122] (scheme 71). TLC analysis indicated that the reaction had given rise to the imine intermediate as well as two new compounds. It seemed to be a clean, albeit slow reaction. The reaction was then left overnight, but no further conversion had taken place. The reaction was stopped and the products isolated. This led to a surprising result. The *trans*-product **80** was, indeed, obtained in 5 %, but the two new compounds were not **78** and **81** as expected. They were identified as the dichloro-analogues **84** (13 %) and **85** (3 %). All three products were contaminated with a yellow by-product (presumably iron residues). A small nOe was observed between H-2 and H-5 in **85** while **84** showed no nOe between these protons. The relative configuration was assigned based on this data.



Scheme 71: The unexpected result from the $FeCl_3$ catalyzed reaction.

The product **84** was found to have essentially the same R_f value as **81**. Therefore the TLC analysis of the reaction had led to the misinterpretation that the reaction was slow, and the low yield may be explained by decomposition due to the prolonged reaction time under harsh conditions. The small amounts of **80**, **84**, and **85** were converted into their TFA salts and used in the standard SOMO-reaction (table 26). The new catalyst **85** performed well with respect to the yield (considering the low catalyst loading due to the limited amount available). The *ee*, however, was lower than those usually observed. This could be caused by the smaller steric bulk of the dichloromethyl group compared to the *tert*-butyl group. Alternatively, since the catalyst was prepared under quite harsh conditions, erosion of the *ee* of the catalyst could have occurred.



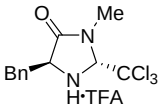
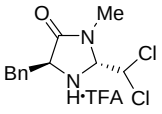
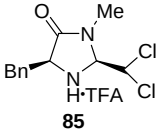
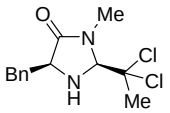
Catalyst	mol%	GC-Yield (%)	d.r.	ee (%)
 **80**	20	none	-	-
 **84**	20	17	n.d.	n.d.
 **85**	15	46	4:1	60

Table 26: Evaluation of 80, 84, and 85 as catalysts.

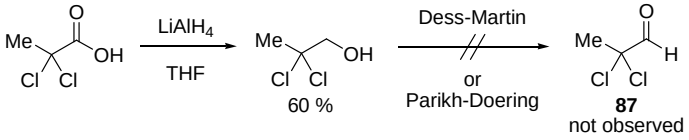
The experience from the catalyst synthesis showed that the trichloromethyl substituent is inherently unstable toward the typical ring-closing conditions. The dichloromethyl derivative should be more stable, and therefore the more bulky analogue **86** (figure 21) was found to be a promising target for further development.



86

Figure 21: 86 was chosen as a promising catalyst structure.

The required 2,2-dichlopropanal (**87**) was not commercially available. The reported syntheses of **87** involve chlorination of propanal.[124] This reaction, however, requires a complex reaction setup, and therefore it was planned to prepare **87** from the corresponding acid instead, which is commercially available (scheme 72). The reduction to the alcohol with $LiAlH_4$ afforded the product in 60 % yield. Oxidation to the aldehyde was attempted with both the Dess-Martin[125] and Parikh-Doering[126] procedures. The Dess-Martin oxidation led to low conversion and several by-products. The aldehyde **87** could not be isolated from the mixture.



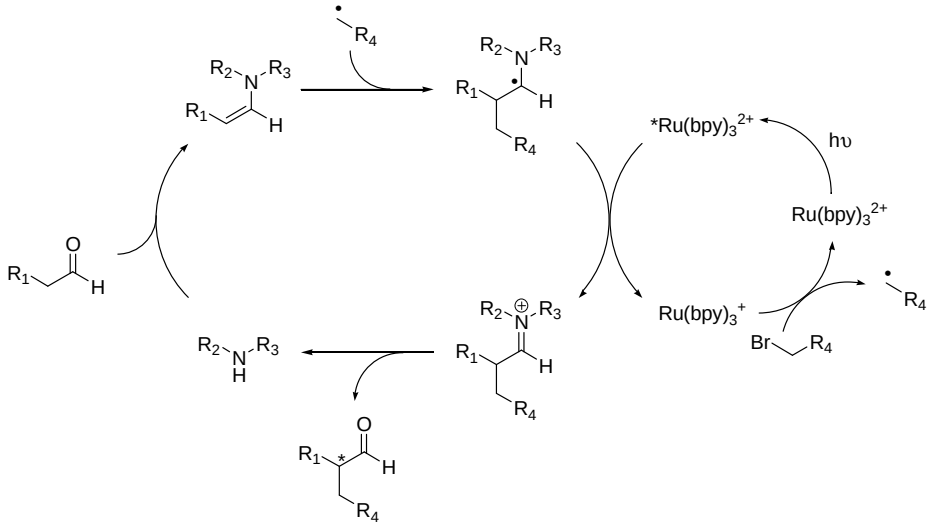
Scheme 72: Attempted synthesis of 88.

The Parikh-Doering oxidation did not give any conversion, and the starting material was recovered. Unfortunately, at this point time was running out, and the synthesis of **86** was never realized.

4.3.6 Photochemical allylation

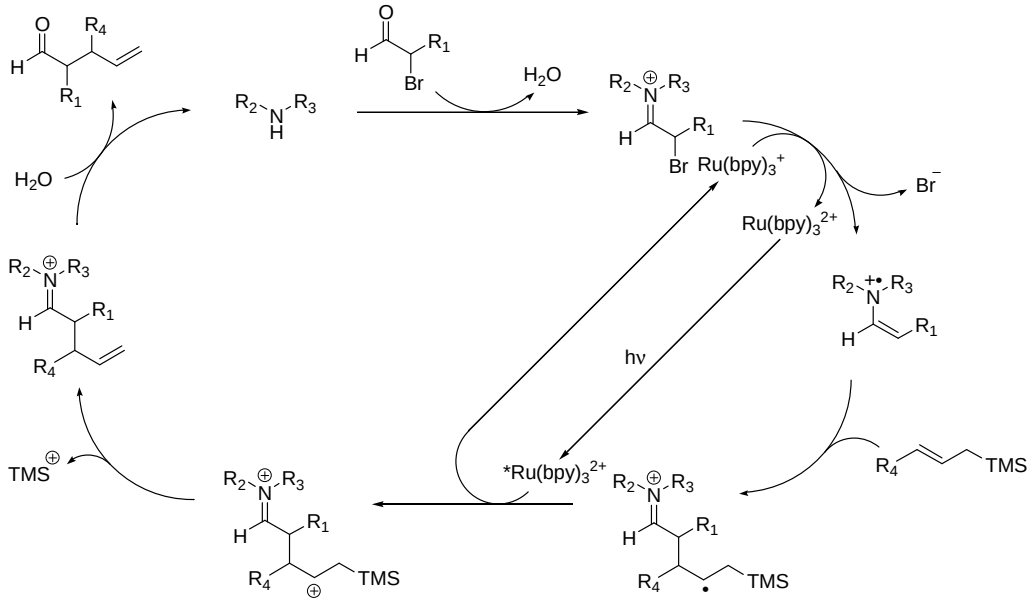
Given the difficulties encountered up to this point, other ways to achieve the same transformation was sought. It has been reported that α-bromocarbonyl compounds can be cleaved photolytically in the presence of a ruthenium trisbipyridyl complex.[127] Recent studies in the MacMillan group has shown that the radical thus generated can react with chiral enamines to generate another radical that can be oxidized by the metal to an

iminium ion which, upon hydrolysis, will release an enantioenriched α–substituted aldehyde (scheme 73).[128]



Scheme 73: Proposed mechanism for the photochemical α-alkylation of aldehydes. Reproduced from ref. 128.

We hoped that by a related mechanism an α-bromoaldehyde could be used to generate a radical that could undergo an allylation reaction. The proposed mechanism for the reaction is shown in scheme 74.

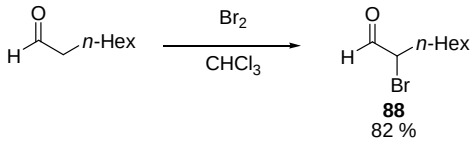


Scheme 74: Proposed mechanism for a photolytic SOMO allylation.

The imidazolidinone catalysts have been found to be compatible with photochemical reactions, and the $Ru(bpy)_3Cl_2$ complex is effectively excited by light with wavelengths around 456 nm.[129] Initially, a Ru(I) species would be needed, and we imagined that this could come from a sacrificial amount of a reductant, *e.g.* enamine. The Ru(I) thus generated could bring about the homolytic cleavage of the C-Br bond. The radical cation intermediate could then react with the allylsilane in the same way as in the standard SOMO reaction (*vide supra*). The excited Ru-complex could serve to oxidize the radical intermediate generating a carbocation that would eliminate the TMS to generate the C-C double bond. The success of the reaction relies on the selective reaction between the iminium ion and the Ru(I) over the homolytic cleavage of the α-bromoaldehyde which could lead to the racemic product. We believed that the cationic character of the iminium ion would make it more reactive toward the Ru(II)* than the neutral aldehyde. To suppress the background reaction we decided to use a small amount of the metal catalyst (0.5 mol% Ru) compared to the organocatalyst (20 mol%). The silyl-cation by-product would be very reactive and addition of water or an alcohol would be necessary to remove this reactive species.

Allylation by this route, of course, requires one extra step for the preparation of the α-bromoaldehyde. However, the photochemical reaction has the obvious advantage in that CAN or other oxidants are avoided, making the overall atom economy more favorable in the photochemical reaction.

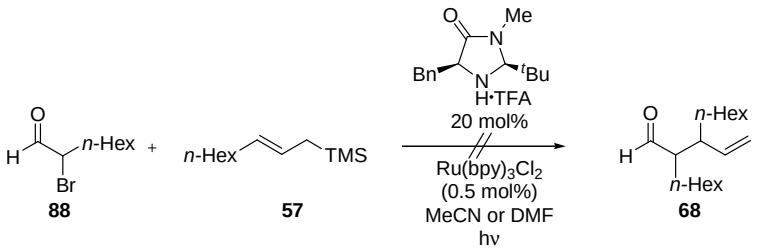
α-Bromooctanal (**88**) was prepared by treating octanal with bromine in $CHCl_3$ (Scheme 75).[130]



88
82 %

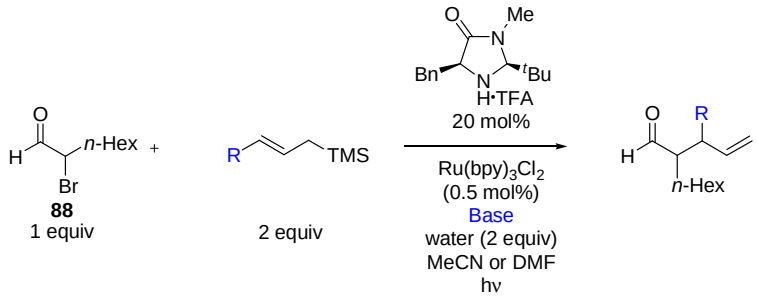
Scheme 75: Synthesis of 88.

First, the photochemical reaction was attempted in DMF and MeCN without any addition of water or base (scheme 76).



Scheme 76: Photochemical SOMO allylation.

GC-analysis analysis of the reaction mixture showed no consumption of the starting materials. Not even the potentially competing reaction between α-bromoaldehyde and allylsilane had taken place under these conditions. The reaction was performed again with addition of water and various bases (table 27).



Entry	Solvent	Base	R	GC-yield (%)	Comments
1	MeCN	$NaHCO_3$	*n*-Hex	0	No consump of start. mat.
2	DMF	$NaHCO_3$	*n*-Hex	0	Allylsilane remained. Aldehyde was consumed.
3	MeCN	2,6-Lutidine	*n*-Hex	0	
4	DMF	2,6-Lutidine	*n*-Hex	0	
5	MeCN	2,6-Lutidine	H	0	
6	DMF	2,6-Lutidine	H	0	

Table 27: Results from the photochemical SOMO allylation.

In most cases the α-bromoaldehyde was completely consumed while the allylsilane remained untouched. The unsubstituted allylsilane was also used (entries 5 and 6) to ensure that the lack of reactivity was not due to the substitution pattern. Since this was also unsuccessful, no further investigations into this reaction were performed.

4.4 Conclusions

A number of 1,2-substituted allylsilanes were synthesized via efficient routes. A SOMO allylation of octanal with some of these allylsilanes was attempted. The initial results showed that the desired product was formed, albeit in low yield. Thorough optimization studies were then undertaken, but the efficiency of the reaction could not be increased beyond 50 % yield, 1:4 d.r. and 94 % *ee*.

The relative stereochemistry was determined by comparison to compounds synthesized by through the Ireland-Claisen rearrangement. Determination of the absolute stereochemistry was not realized, but this could easily be done via several reaction routes.

Next, considerable work was done to clarify why the yields could not be improved. It was found that the catalyst was consumed under the reaction conditions. These studies indicated that the catalyst was oxidized in the 2-position before further degradation. Final evidence for this pathway could, however, not be obtained.

Design and synthesis of a more robust catalyst was then commenced, and the catalyst **85** did, indeed, lead to a higher yield, however, a decrease in *ee* was observed. The synthesis of an improved version (**86**) was attempted, but due to time constraints the synthesis was not realized.

Finally, the development of a photochemical version of the allylation was initiated. The initial results were not encouraging, and the idea was abandoned.

5 Summary

Three projects in the area of method development in catalysis were carried out.

The first project dealt with the synthesis of *N*-heterocycles from diols and amines catalyzed by the commercially available $[Cp^*IrCl_2]_2$ complex. Several types of *N*-heterocycles were targeted, but most of the planned syntheses were unsuccessful. The exception is the important piperazine unit, for which we developed an environmentally friendly synthesis with good atom economy and water as the only by-product.

The second project was based the serendipitous discovery that Ru(II)-NHC-phosphine complexes can catalyze the formation of amides from alcohols and amines by extrusion of hydrogen gas. The catalytic system was optimized with respect to the ligands, and the reaction was found to be applicable to a wide range of substrates. This reaction also proceeds with excellent atom economy and is therefore a very environmentally friendly alternative to existing methods.

The final project was the development of an organocatalytic allylation of aldehydes with 1,2-disubstituted allylsilanes. Thorough optimization studies were undertaken, but useful yields could not be obtained, even though the d.r. was acceptable (1:4) and the *ee* was high (94 %). Development of a novel catalyst was commenced, and a promising lead was identified. Unfortunately, further development of this was made impossible due to time constraints.

6 Experimental section

6.1 Work done at DTU

General methods:

All chemicals were purchased from Aldrich and used without further purification. Exceptions include: $[Cp^*IrCl_2]_2$ which was either synthesized by a literature procedure[131] or purchased from Strem. Silver(I) oxide was prepared from silver nitrate and stored in a dark bottle in a dessicator.[132] $PCyp_3 \cdot HBF_4$ was prepared by a literature procedure.[83] JohnPhos, DavePhos and XPhos were donated by Saltigo GmbH, Germany. The triazolium salt, 6,7-dihydro-2-phenyl-5*H*-pyrrolo[2,1-c]-1,2,4-triazolium chloride was purchased from ABCR. Some partially protected carbohydrates were available in the DTU stock room.

Toluene, diethyl ether and THF were distilled form sodium and benzophenone under nitrogen. CH_2Cl_2 was dried over calcium hydride and distilled under nitrogen.

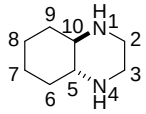
Mass spectrometry was performed by direct inlet on a Shimadzu GCMS-QP5000 instrument. HRMS were recorded at the Department of Chemistry, University of Copenhagen (ionization method: ESP+). IR spectra were recorded on a Bruker alpha-P spectrometer. ^1H and ^{13}C NMR spectra obtained on a Varian Mercury 300 instrument at 300 MHz and 75 MHz, respectively. The spectra were calibrated using residual solvent signals[133] or TMS. GC yields were measured on a Shimadzu GC2010 equipped with an Equity™ 1 column and with dodecane as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Column chromatography was performed on silica gel (220–440 mesh).

6.1.1 Iridium catalyzed N-heterocyclizations

6.1.1.1 General method for synthesis of piperazines

A heavy-walled flask was charged with $[Cp^*IrCl_2]_2$ (8 mg, 10 μmol), $NaHCO_3$ (10 mg, 0.12 mmol), diamine (2 mmol), diol (2 mmol), and solvent (1 mL). The flask was then purged with argon, sealed and heated in an aluminum block overnight. After cooling to r.t. K_2CO_3 (aq.) and CH_2Cl_2 were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic phases were dried over

K_2CO_3, filtered and concentrated. The residue was purified by column chromatography (eluent: heptane/EtOAc or MeOH/CH_2Cl_2 mixtures) to give the desired products.



2

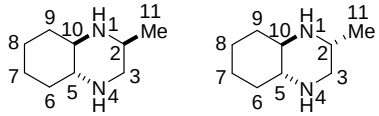
(±)-*trans*-Decahydroquinoxaline (2)

Yield: 96 (H_2O); 94 % (PhMe).

^{1}H NMR ($CDCl_3$): δ 2.98–2.78 (m, 4H), 2.25–2.10 (m, 2H), 1.80–1.10 (m, 10H, H-1, H-4, H-6, H-7, H-8, H-9).

^{13}C NMR ($CDCl_3$): δ 61.4 (C-5, C-10), 47.1 (C-2, C-3), 32.1 (C-6, C-9), 25.0 (C-7, C-8).

MS: *m/z* 140 [M].



Major Minor

(±)-(2*S*,4a*R*,8a*R*)-Decahydro-2-methylquinoxaline

Yield: 98; >20:1 d.r. (H_2O); 87 % 3:1 d.r. (PhMe).

^{1}H NMR ($CDCl_3$): δ 2.88 (dd, 1H, *J* = 2.9 Hz, *J* = 11.6 Hz, H-3eq), 2.83–2.73 (ddq, 1H, *J* = 2.9 Hz, *J* = 6.3 Hz, *J* = 10.0 Hz, H-2), 2.38 (dd, 1H, *J* = 10.2 Hz, *J* = 11.6 Hz, H-3ax), 2.26–2.05 (m, 2H, H-5, H-10), 1.75–1.55 (m, 6H, H-1, H-4, H-6, H-9), 1.30–1.05 (m, 4H, H-7, H-8), 0.96 (d, 3H, *J* = 6.3 Hz, H-11).

^{13}C NMR ($CDCl_3$): δ 61.7, 60.7 (C-5, C-10), 54.2, 52.2 (C-2, C-3), 32.2, 32.0 (C-6, C-9), 25.2, 25.0 (C-7, C-8), 20.0 (C-11).

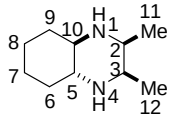
HRMS calcd. for $C_9H_{19}N_2$ $[M+H]^+$ *m/z* 155.1548, found *m/z* 155.1556.

Minor isomer

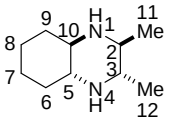
^{1}H NMR ($CDCl_3$): δ 3.41 (tq, 1H, *J* = 1.8 Hz, *J* = 7.0 Hz, H-2), 2.58–2.47 (m, 2H, H-3ax, H-3eq), 2.16–2.07 (m, 2H, H-5, H-10), 1.85–1.05 (m, 8H, H-6, H-7, H-8, H-9), 0.96 (d, 3H, *J* = 6.6 Hz, H-11).

^{13}C NMR ($CDCl_3$): δ 62.9, 60.8 (C-5, C-10), 56.5, 50.0 (C-2, C-3), 32.3, 32.0 (C-6, C-9), 25.1, 24.9 (C-7, C-8), 18.3 (C-11).

MS: *m/z* 154 [M].



Major



Minor

(±)-(2*R*,3*S*,4a*R*,8a*R*)-Decahydro-2,3-dimethylquinoxaline (major isomer)

Yield: 81; 3:1 d.r. (H_2O); 79 %; 1:1 d.r. (PhMe).

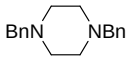
^{1}H NMR ($CDCl_3$): δ 3.05, 2.88 (2 × dq, 1H each, *J* = 3.6 Hz, *J* = 6.7 Hz, H-2, H-3), 2.44–2.15 (m, 2H, H-5, H-10), 1.67–1.50 (m, 6H, H-1, H-4, 2 × H-6, 2 × H-9), 1.30–1.15 (m, 4H, 2 × H-7, 2 × H-8), 1.08, 0.91 (2 × d, 3H each, *J* = 6.7 Hz, H-11, H-12).

^{13}C NMR ($CDCl_3$): δ 62.6, 54.4, 53.4, 52.1 (C-2, C-3, C-5, C-10), 31.2, 31.9 (C-6, C-9), 25.0, 24.9 (C-7, C-8), 19.2 (C-11), 12.8 (C-12).

HRMS calcd. for $C_{10}H_{21}N_2$ $[M+H]^+$ *m/z* 169.1705, found *m/z* 169.1705.

Minor isomer

^{13}C NMR ($CDCl_3$): δ 61.3 (C-5, C-10), 57.9 (C-2, C-3), 31.7 (C-6, C-9), 19.0 (C-11, C-12).



1,4-Dibenzylpiperazine

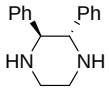
Yield: 73 (H_2O); 74 % (PhMe); (94 % when synthesized from $BnNH_2$ neat).

^{1}H NMR ($CDCl_3$): δ 7.35–7.21 (m, 10H, Ar), 3.52 (s, 4H, Ph-C*H*$_2$-N), 2.49 (bs, 8H, N-*C*H$_2$-*C*H$_2$-N).

^{13}C NMR ($CDCl_3$): δ 138.2, 129.4, 128.3, 127.1 (Ar), 63.2 (Ph-*C*H$_2$-N), 53.2 (N-*C*H$_2$-*C*H$_2$-N)

MS: *m/z* 266 [M].

For literature data, see reference 134.



(2*S*,3*S*)-2,3-Diphenylpiperazine

Yield: 86 (H_2O with TFA); 54 % (PhMe).

$[\alpha]_D^{25}$ = -102 (*c* 1.0, $CHCl_3$) (lit.[135] $[\alpha]_D^{25}$ = -104.6 (*c* 1.0, $CHCl_3$)).

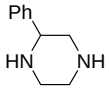
Mp 93–95 °C (lit.[135] Mp 94–96 °C).

^{1}H NMR ($CDCl_3$): δ 7.20–7.05 (m, 10H, Ar), 3.71 (s, 2H, H-2, H-3), 3.14 (s, 4H, H-5, H-6), 2.01 (bs, 2H, H-1, H-4).

^{13}C NMR ($CDCl_3$): δ 141.5 (C_{ipso}), 128.1, 127.9, 127.3 (Ar), 68.3 (C-2, C-3), 47.2 (C-5, C-6).[135]

MS: *m/z* 238 [M].

The starting material, (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane, was prepared by resolution[136] and showed an optical rotation of $[\alpha]_D^{25}$ = -104 (*c* 1.5, MeOH) (lit.[136] $[\alpha]_D^{23}$ = -106 (*c* 1.1, MeOH)).



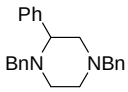
(±)-2-Phenylpiperazine

Yield: quant. (H_2O).

^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 5H, Ar), 3.73 (dd, 1H, *J* = 2.8 Hz, *J* = 10.2 Hz, H-2), 3.11–2.80 (m, 5H, H-3eq, H-5ax, H-5eq, H-6ax, H-6eq), 2.69 (dd, 1H, *J* = 10.2 Hz, *J* = 11.9 Hz, H-3ax), 1.80 (bs, 2H, N-*H*).

^{13}C NMR ($CDCl_3$): δ 142.8 (C_{ipso}), 128.5, 127.5, 126.9 (Ar), 62.1 (C-2), 54.4, 47.9, 46.1 (C-3, C-4, C-5).[137]

HRMS calcd. for $C_{10}H_{15}N_2$ [M+H] *m/z* 163.1235, found *m/z* 163.0981.



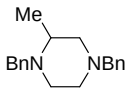
(±)-1,4-Dibenzyl-2-phenylpiperazine

Yield: 93 %.

^{1}H NMR ($CDCl_3$): δ 7.45–7.10 (m, 15H, Ar), 3.71 (d, 1H, *J* = 13.4 Hz, Ph-C*H*H'-N), 3.43 (s, 2H, Ph-CH_2-N), 3.36 (dd, 1H, *J* = 3.0 Hz, *J* = 10.3 Hz, H-2), 2.85–2.67 (m, 4H, Ph-CH*H*'-N, H-3eq, H-5, H-6), 2.25–2.05 (m, 3H, H-3ax, H-5', H-6').

^{13}C NMR ($CDCl_3$): δ 142.3, 139.2, 138.0 (3 × C_{ipso}), 129.3, 128.9, 128.6, 128.3, 128.2, 127.5, 127.1, 126.8 (Ar), 67.4 (C-2), 63.1 (N-*C*H_2-Ph), 62.1 (C-4 or C-5), 59.1 (N-*C*H_2-Ph), 53.3 (C-4 or C-5), 51.9 (C-3).

HRMS calcd. for $C_{24}H_{27}N_2$ [M+H] *m/z* 343.2174, found *m/z* 343.2153.



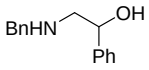
(±)-1,4-Dibenzyl-2-methylpiperazine

Yield: 63 %.

^{1}H NMR ($CDCl_3$): δ 7.35–7.20 (m, 10H, Ar), 4.05 (d, 1H, *J* = 13.3 Hz, Ph-C*H*H'-N), 3.48 (s, 2H, Ph-CH_2-N), 3.19 (d, 1H, *J* = 13.2 Hz, Ph-CH*H*'-N), 2.75–2.60 (m, 3H, H-3eq, H-5, H-6), 2.50 (dqd, 1H, *J* = 3.0 Hz, *J* = 6.2 Hz, *J* = 9.1 Hz, H-2), 2.26–2.12 (m, 2H, H-5', H-6'), 2.02 (dd, 1H, *J* = 9.7 Hz, *J* = 10.5 Hz, H-3ax), 1.14 (d, 3H, *J* = 6.2 Hz, -CH_3).

^{13}C-NMR (C_6D_6): δ 140.1, 139.3 (2 × C_{ipso}), 129.2, 129.1, 128.5, 128.4 (2 × C_{ortho}, 2 × C_{meta}), 127.2, 127.0 (2 × C_{para}), 63.3, 61.1, 58.5, 55.7, 53.9, 51.5 (2 × Ph-*C*H_2-N, C-2, C-3, C-5, C-6), 16.7 (bs, -*C*H_3).

HRMS calcd. for $C_{19}H_{25}N_2$ $[M+H]^+$ *m/z* 281.2018, found *m/z* 281.2026.



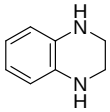
2-(Benzylamino)-1-phenylethanol

Yield: 67 %.

^{1}H NMR ($CDCl_3$): δ 7.37–7.21 (m, 10H, Ar), 4.72 (dd, 1H, *J* = 3.6 Hz, *J* = 8.9 Hz, -C*H*(Ph)-OH), 3.84 (d, 1H, *J* = 13.3 Hz, Ph-C*H*H'-), 3.78 (d, 1H, *J* = 13.3 Hz, Ph-CH*H*'), 2.91 (dd, 1H, *J* = 3.6 Hz, *J* = 12.1 Hz, N-C*H*H'-CH(Ph)-), 2.74 (dd, 1H, *J* = 8.9 Hz, *J* = 12.2 Hz, N-CH*H*'-CH(Ph)-), 2.70 (bs, 2H, -O-*H*, N-*H*).

^{13}C NMR ($CDCl_3$): δ 142.7, 140.0, 128.6, 128.5, 128.2, 127.6, 127.2, 125.9 (Ar), 71.9 (-*C*H(Ph)-OH), 56.7, 53.6 (2 × -*C*H_2-).[138]

MS: *m/z* 228.1 [M+H].



1,2,3,4-Tetrahydroquinoxaline

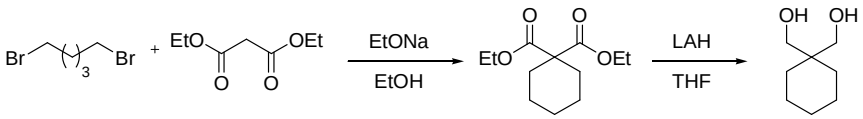
Yield: 13 %.

^{1}H NMR ($CDCl_3$): δ 6.61–6.55 (m, 2H, Ar), 6.52–6.47 (m, 2H, Ar), 3.42 (s, 4H, 2 × -C*H*$_2$-).

^{13}C NMR ($CDCl_3$): δ 133.8, 118.9, 114.8 (Ar), 41.5 (N-*C*H_2-).[139]

MS: *m/z* 135 [M+H].

6.1.1.2 Synthesis of substrates



1,1-Di(hydroxymethyl)cyclohexane

Sodium (0.6 g, 25 mmol) was added to EtOH (10 mL) under a nitrogen atmosphere. The sodium was allowed to react completely before diethylmalonate (2 g, 12.4 mmol) and more EtOH (5 mL) were added. The mixture was stirred for 15 min. and 1,5-dibromopentane (3.16 g, 137 mmol, 1.87 mL) was added drop-wise. The reaction mixture was then heated to reflux and kept at this temperature for 3 hours followed by 16 hours at room temperature. The solvent was removed *in vacuo* and the residue was taken up in water and extracted with Et_2O (5 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The product was isolated by distillation under reduced pressure. This yielded 1.50 g (6.6 mmol; 53 %) of the product as a clear oil, containing a minor impurity.

^{1}H NMR ($CDCl_3$): δ 4.06 (4H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 1.89–1.82 (4H, m, C(C*H*$_2$CH$_2$)$_2$CH$_2$), 1.45–1.27 (6H, m, (C(CH$_2$C*H*$_2$)$_2$C*H*$_2$), 1.12 (6H, t, (OCH$_2$C*H*$_3$).

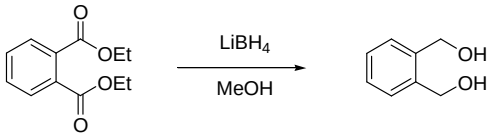
^{13}C NMR ($CDCl_3$): δ 171.7 (*C*=O), 60.9 (O-*C*H$_2$-CH$_3$), 54.7 (*C*-(COOEt)$_2$), 31.2 (C-*C*H$_2$), 25.1 (C-CH$_2$-*C*H$_2$), 22.6 (C-CH$_2$-CH$_2$-*C*H$_2$), 13.9 (-*C*H$_3$)

Literature procedure: see reference 140.

The diester (200 mg, 0.88 mmol) was dissolved in THF (5 mL) and added drop-wise over 20 min. to a suspension of LAH (73 mg, 1.9 mmol) in THF (10 mL) at 5 °C. The resulting mixture was stirred at room temperature for 3 hours and then cooled to 0 °C before EtOAc (5 mL) was added and the mixture was poured into 2 M HCl (15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (5 × 15 mL). The combined organic phases were washed with brine and dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: EtOAc/heptane 1:1). Yield: 90 %.

^{1}H NMR ($CDCl_3$): δ 3.62 (s, 4H, -C*H*$_2$OH), 2.14 (s, 2H, -O*H*), 1.48–1.31 (m, 10H, 5 × -C*H*$_2$-).

^{13}C NMR ($CDCl_3$): δ 70.6 (-*C*H$_2$OH), 38.4 (*C*-(CH$_2$-OH)$_2$), 29.7 (C-*C*H$_2$-CH$_2$), 26.6 (C-CH$_2$-*C*H$_2$-), 21.5 (C-CH$_2$-CH$_2$-*C*H$_2$-).



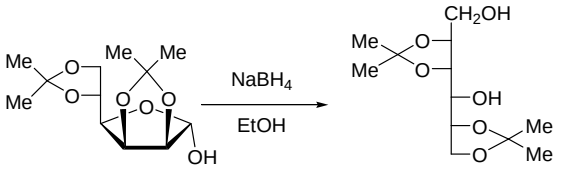
1,2-Di(hydroxymethyl)benzene

An oven-dried flask under nitrogen atmosphere was charged with Et_2O (60 mL), $LiBH_4$ (2 M in THF, 20 mL, 40 mmol), diethyl phthalate (3 g, 13 mmol), and MeOH (1.6 mL, 40 mmol). The mixture was then heated to reflux temperature for 20 min. at which time TLC analysis (eluent: heptane/EtOAc 1:1) showed complete consumption of the starting material. The reaction mixture was then cooled in an ice bath and the reaction was quenched by careful addition of 1 M HCl (30 mL). The resulting mixture was stirred for 20 min. and diluted with water, extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The title compound was obtained as a white solid (1.53 g, 11 mmol, 83 %).

^{1}H-NMR ($CDCl_3$): δ 7.31 (s, 4H, Ar), 4.65 (s, 4H, -C*H*$_2$OH), 3.38 (s, 2H, -O*H*).

^{13}C-NMR ($CDCl_3$): δ 139.5, 129.8, 128.7 (Ar), 64.2 (-*C*H$_2$OH).

Literature procedure: see ref. 141. For NMR data see ref. 142.

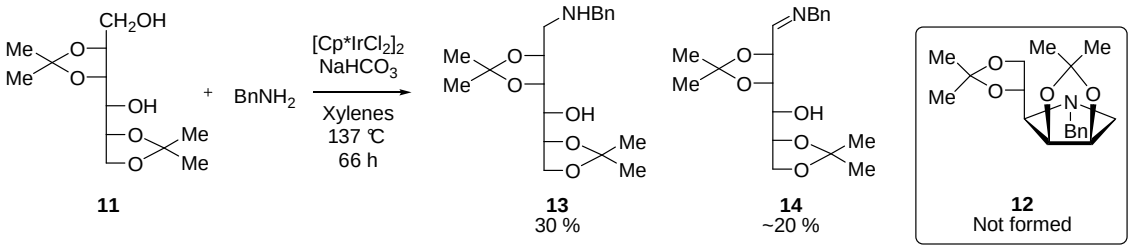


2,3:5,6-Di-*O*-isopropylidene-D-mannitol (11)

$NaBH_4$ (991 mg, 26.2 mmol) was dissolved in EtOH (60 mL) at r.t. and the mannofuranose (6.6 g, 25.2 mmol) was added in small portions. The solution was stirred at r.t. for 40 min. before NH_4Cl (~1 g) was added. The stirring was continued for another 30 min. The solvent was then removed and the residue was taken up in water. The product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give the product in 96 % yield (6.38 g).

^{1}H-NMR ($CDCl_3$): δ 4.38 (dd, 1H, *J* = 1.5 Hz, *J* = 7.3 Hz), 4.30 (td, 1H, *J* = 4.3 Hz, *J* = 7.3 Hz), 4.15–3.98 (m, 3H), 3.95–3.75 (m, 2H), 3.57 (t, 1H, *J* = 6.4 Hz), 3.20 (d, 1H, *J* = 6.2 Hz), 2.85–2.73 (m, 1H), 1.51, 1.40, 1.39, 1.35 (4 × s, 3H each, 4 × -C*H*$_3$).[143]

^{13}C-NMR ($CDCl_3$): δ 109.5, 108.5 (*C*Me$_2$), 77.1, 76.1, 75.8, 70.4, 67.4, 60.9 (C-1, C-2, C-3, C-4, C-5, C-6), 26.9, 26.8, 25.3, 24.9 (4 × -*C*H$_3$).



Attempted synthesis of

1-benzyl-1,4-dideoxy-1,4-imino-2,3:5,6-di-*O*-isopropylidene-D-mannitol (12)

The mannitol **11** (535 mg, 2.0 mmol) was added to xylenes (0.3 mL) in a heavy walled flask followed by $BnNH_2$ (0.33 mL, 3.0 mmol), $[Cp^*IrCl_2]_2$ (20 mg, 0.025 mmol), and $NaHCO_3$ (5 mg, 0.6 mmol). The flask was then purged with nitrogen, sealed, and heated to 137 °C for 66 hours. After cooling to r.t. the reaction mixture was concentrated and the

residue was purified by column chromatography (eluent: heptane/EtOAc 1:1 → 2:3). This gave **13** (30 %) and **14** (~20 %, some impurity remained by ^{1}H NMR).

13:

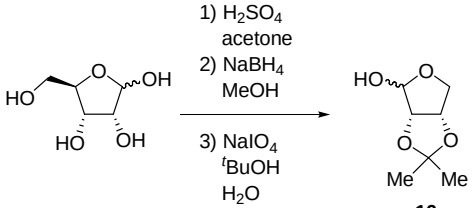
^{1}H-NMR ($CDCl_3$): δ 7.28–7.16 (m, 5H, Ar), 4.14 (td, 1H, *J* = 5.3 Hz, *J* = 8.4 Hz), 4.04–3.92 (m, 4H), 3.80 (d, 1H, *J* = 13.4 Hz, Ph-C*H*H'), 3.75 (d, 1H, *J* = 13.4 Hz, Ph-CH*H*'), 3.43 (dd, 1H, *J* = 1.9 Hz, *J* = 6.8 Hz), 2.76 (d, 2H, *J* = 5.3 Hz), 2.25 (bs, 2H, -N*H*Bn, -O*H*), 1.36 (s, 6H, 2 × -CH_3), 1.34, 1.28 (2 × s, 3H each, 2 × -CH_3).

^{13}C-NMR ($CDCl_3$): δ 140.0, 128.5, 128.1, 127.1 (Ar), 109.4, 109.3 (*C*Me_2), 78.8, 76.5, 76.4, 70.5, 67.1, 54.0, 50.7 (C-1, C-2, C-3, C-4, C-5, C-6, Ph-*C*H_2-), 27.5, 27.0, 26.9, 25.4 (4 × -*C*H_3).

14:

^{1}H-NMR ($CDCl_3$): δ 7.49–7.22 (m, 5H, Ar), 7.00–6.88 (m, 1H, *H*C=N), 4.67 (dd, 1H, *J* = 0.6 Hz, *J* = 8.3 Hz), 4.68 (d, 1H, *J* = 8.3 Hz), 4.47 (t, 2H, *J* = 5.6 Hz), 4.10–3.94 (m, 5H), 1.52, 1.41, 1.39, 1.35 (4 × s, 3H each, 4 × -CH_3).

^{13}C-NMR ($CDCl_3$): δ 170.1 (*C*=N), 137.9, 128.8, 127.8, 127.6 (Ar), 109.8, 109.5 (*C*Me_2), 76.6, 76.0, 75.5, 69.2, 67.3 (C2, C3, C4, C5, C6), 43.1 (Ph-*C*H_2-), 26.9, 26.5, 25.5, 24.4 (4 × -*C*H_3).



16

2,3-*O*-Isopropylidene-L-erythrose (16)

D-Ribose (8.2 g, 54.6 mmol) was suspended in acetone (80 mL) and conc. H_2SO_4 (0.2 mL) was added. After one hour the solids were completely dissolved and the solution was stirred for an additional two hours before it was neutralized by addition of $Ca(OH)_2$ (1.09 g, 14.7 mmol). The mixture was filtered through Celite® and the volatiles were removed under reduced pressure. The oily residue was directly used for the next reaction without purification.

To the crude product was added MeOH (70 mL) and the solution was cooled in an ice bath. $NaBH_4$ (3.4 g, 89 mmol) was then added in portions (temperature was kept below 5 °C). After complete addition the stirring was continued for two hours at room temperature. Removal of the solvent gave a white foam that was dissolved in ^{t}BuOH/water (3:2; 170 mL) and $NaIO_4$ (48 g, 225 mmol) was added in portions. The resulting solution was stirred overnight before CH_2Cl_2 (170 mL) was added and the mixture was neutralized by addition of $NaHCO_3$. The solids were filtered off and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 70 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated to give an oily residue which was purified by column chromatography (eluent: heptane/EtOAc 3:1 → 1:1). The desired compound was obtained as a colorless oil (5.18 g, 32.4 mmol, 59 % over three steps) containing a 1:10 mixture of anomers.

Major anomer:[144]

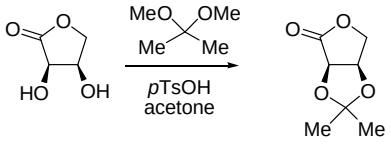
^{1}H-NMR ($CDCl_3$): δ 5.41 (s, 1H, H-1), 4.83 (ddd, 1H, *J* = 0.4 Hz, *J* = 3.4 Hz, *J* = 5.9 Hz, H-3), 4.57 (d, 1H, *J* = 5.9 Hz, H-2), 4.07 (dd, 1H, *J* = 3.4 Hz, *J* = 10.4 Hz, H-4a), 4.01 (dd, 1H, *J* = 0.6 Hz, *J* = 10.4 Hz, H-4b), 3.06 (s, 1H, -O*H*), 1.46, 1.31 (2 × s, 3H each, 2 × -CH_3).

^{13}C-NMR ($CDCl_3$): δ 112.4 (*C*Me_2), 101.9 (C-1), 85.2 (C-2), 80.0 (C-3), 72.0 (C-4), 26.3, 24.8 (2 × -*C*H_3).

Minor anomer:

^{1}H-NMR ($CDCl_3$): δ 4.99 (dd, 1H, *J* = 3.5 Hz, *J* = 11.4 Hz, H-4a), 4.75 (ddt, 1H, *J* = 0.6 Hz, *J* = 3.7 Hz, *J* = 6.2 Hz, H-2), 4.48 (dd, 1H, *J* = 3.7 Hz, *J* = 6.2 Hz, H-3), 3.54 (ddd, 1H, *J* = 0.4 Hz, *J* = 3.7 Hz, *J* = 11.1 Hz, H-4b), 1.54, 1.37 (2 × s, 3H each, 2 × -CH_3). H-1 and –O*H* were not observed due to the low intensity of the signals of the minor anomer.

^{13}C-NMR ($CDCl_3$): δ 113.5 (*C*Me_2), 97.6 (C-1), 79.7 (C-2), 78.3 (C-3), 67.7 (C-4), 26.1, 25.0 (2 × -*C*H_3).



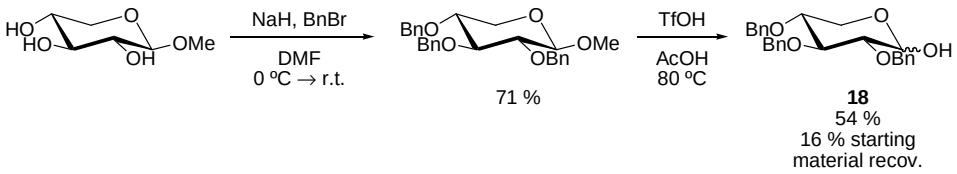
***ent*-17**

2,3-*O*-Isopropylidene-D-erythrono-1,4-lactone (*ent*-17)

D-Erythrono-1,4-lactone (2.21 g, 18.7 mmol), acetone (15 mL), 2,2-dimethoxypropane (30 mL), and *p*-TsOH (0.3 g) were added to a flask and the resulting solution was stirred for 6 hours and then quenched with aq. ammonia (24 %, 3 mL). The volatiles were removed under reduced pressure, and the resulting clear oil was dissolved in Et_2O and $MgSO_4$ was added. After 5 min. the solids were removed by filtration through Celite®. Concentration and further drying under high vacuum gave the desired lactone as a white solid (91 %).

^{1}H-NMR ($CDCl_3$): δ 4.87 (ddd, 1H, *J* = 1.1 Hz, *J* = 3.3 Hz, *J* = 5.6 Hz, H-3), 4.74 (d, 1H, *J* = 5.6 Hz, H-2), 4.45 (dd, 1H, *J* = 1.0 Hz, *J* = 11.0 Hz), H-4), 4.40 (dd, 1H, *J* = 3.3 Hz, *J* = 11.0 Hz, H-4'), 1.49, 1.40 (2 × s, 3H each, 2 × -CH_3).[145]

^{13}C-NMR ($CDCl_3$): δ 174.3 (*C*=O), 114.1 (*C*Me_2), 75.6, 74.7, 70.3 (C-2, C3, C-4), 26.9, 25.7 (2 × -*C*H_3).



2,3,4-Tri-*O*-benzyl-D-xylopyranose (18)

Methyl β-D-xylopyranoside (2.06 g, 12.5 mmol) was dissolved in DMF (70 mL) under argon atmosphere at 0 °C. NaH (60 % oil suspension, 3.6 g, 75.3 mmol) was added and the reaction mixture was stirred for 20 min. BnBr (6.72 mL, 9.66 g, 56.5 mmol) was then added and the mixture was stirred at room temperature overnight. The reaction was quenched by careful addition of water. The solution was diluted with EtOAc (100 mL), the phases were separated and the organic phase was washed with water (5 × 40 mL). The organic phase was then dried over $MgSO_4$, filtered, and concentrated. The benzylated product was obtained after column chromatography (eluent heptane/EtOAc 20:1 then 3:1). Yield: 3.87 g (8.90 mmol, 71 %).

^{1}H-NMR ($CDCl_3$): δ 7.40–7.24 (m, 15H, Ar), 4.89 (d, 1H, *J* = 11.2 Hz, Ph-C*H*H'), 4.88–4.86 (m, 2H, Ph-CH_2-), 4.75 (d, 1H, *J* = 10.0 Hz, Ph-C*H*H'), 4.71 (d, 1H, *J* = 9.4 Hz, Ph-C*H*H'), 4.63 (d, 1H, *J* = 11.6 Hz, Ph-CH*H*'), 4.26 (d, 1H, *J* = 7.6 Hz, H-1), 3.95 (dd, 1H, *J* = 4.8 Hz, *J* = 11.5 Hz, H-4eq), 3.65–3.54 (m, 5H, H-3, H-4, -CH_3), 3.36 (dd, 1H, *J* = 7.6 Hz, *J* = 8.9 Hz, H-2), 3.22 (dd, 1H, *J* = 9.7 Hz, *J* = 11.5 Hz, H-4ax).

^{13}C-NMR ($CDCl_3$): δ 138.7, 138.6, 138.2, 128.6, 128.4, 128.1, 128.1, 128.0, 128.7 (Ar), 105.4 (C-1), 83.7 (C-3), 82.0 (C-2), 78.0 (C-4), 75.7 (Ph-*C*H_2-), 75.0 (Ph-*C*H_2-), 73.5 (Ph-*C*H_2-), 64.0 (C-5), 57.1 (O-*C*H_3). For the assignment, see ref. 146.

The benzylated xylopyranoside (0.70 g, 1.62 mmol) was dissolved in AcOH (16 mL) and aqueous TfOH (0.5 mL, in 2.3 mL water, ~2 M) was added. The mixture was then heated to 80 °C and stirred for 3 hours. After cooling to r.t. CH_2Cl_2 (40 mL) was added and the resulting solution was poured into cold sat. $NaHCO_3$ (50 mL) and stirred for 45 min. The phases were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated. The remaining solid was purified by column chromatography (eluent: heptane/EtOAc 3:20), and the desired product was obtained as a mixture of anomers (370 mg, 0.88 mmol, 54 %) along with the starting material (110 mg, 0.25 mmol, 16 %).

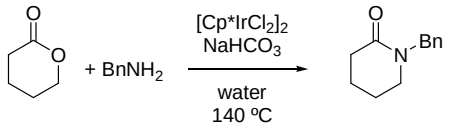
Major anomer:

^{1}H-NMR ($CDCl_3$): δ 7.40–7.26 (m, 15H, Ar), 5.11 (d, 1H, *J* = 3.5 Hz, H-1), 4.87–4.85 (m, 2H, Ph-CH_2-), 4.78 (d, 1H, *J* = 11.7 Hz, PhC*H*H'-), 4.73 (d, 1H, *J* = 11.7 Hz, PhC*H*H'-), 4.67 (d, 1H, *J* = 11.4 Hz, PhCH*H*'-), 4.64 (d, 1H, *J* = 11.6 Hz, PhCH*H*'-), 3.85 (d, 1H, *J* = 8.6 Hz), 3.79 (d, 1H, *J* = 10.4 Hz), 3.71–3.54 (m, 2H), 3.49 (dd, 1H, *J* = 3.5 Hz, *J* = 8.9 Hz, H-5').

^{13}C-NMR ($CDCl_3$): δ 138.7, 138.3, 137.9, 128.6, 128.6, 128.5, 128.5, 128.2, 128.1, 127.9, 127.9, 127.8 (Ar), 91.6 (C-1), 80.6, 79.5, 77.6, 75.6, 73.5, 73.3 (C-2, C-3, C-4, 3 × Ph-*C*H_2-), 60.5 (C-5).[147]

Minor anomer:

^{13}C-NMR ($CDCl_3$): δ 138.6, 138.4, 138.2, 128.2, 128.1, 128.0 (Ar), 97.9 (C-1), 83.3, 82.3, 77.6, 74.9, 73.4, 63.8. Other signals coincide with the major anomer.



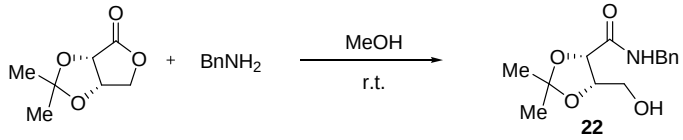
1-Benzylpiperidin-2-one (19b)

A heavy-walled flask was charged with $[Cp^*IrCl_2]_2$ (8 mg, 10 μmol), $NaHCO_3$ (10 mg, 0.12 mmol), benzylamine (0.22 mL, 214 mg, 2 mmol), δ-valerolactone (0.19 mL, 200 mg, 2 mmol), and water (1 mL). The flask was then purged with argon, sealed and heated to 140 °C in an aluminum block overnight. After cooling to r.t. K_2CO_3 (saturated aq., 5 mL) and CH_2Cl_2 (15 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried over K_2CO_3, filtered and concentrated. The residue was purified by column chromatography (eluent: heptane/EtOAc 1:1) to give the desired lactam (143 mg, 0.75 mmol, 38 %).

^{1}H-NMR ($CDCl_3$): δ 7.28–7.14 (m, 5H, Ar), 4.52 (s, 2H, Ph-*C*H_2-N), 3.11 (t, 1H, *J* = 5.7 Hz, N-C*H*$_2$-CH_2), 2.39 (t, 1H, *J* = 6.3 Hz, O=C-C*H*$_2$), 1.75–1.63 (m, 4H, N-CH_2-C*H*$_2$- C*H*$_2$).

^{13}C-NMR ($CDCl_3$): δ 169.9 (*C*=O), 137.3, 128.6, 128.0, 127.3 (Ar), 50.1 (Ph-*C*H_2-N), 47.3 (N-*C*H_2-CH_2), 32.4 (O=C-*C*H_2), 23.2 (O=C-CH_2-*C*H_2), 21.4 (N-CH_2-*C*H_2).

MS: *m/z* 189 [M].



22

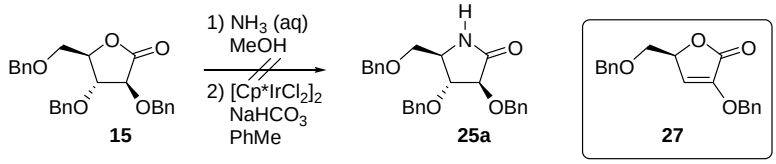
(4*S*,5*S*)-*N*-benzyl-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamide (22)

The lactone (25 mg, 0.16 mmol) was dissolved in MeOH (3 mL) and benzylamine (21 μL, 0.19 mmol) was added. The resulting solution was stirred at r.t. for two hours. Removal of the solvent gave a colorless oil that was analyzed by NMR.

^{1}H-NMR ($CDCl_3$): δ 7.45–7.25 (m, 5H, Ar), 7.10 (bs, 1H, N-*H*), 4.67 (d, 1H, *J* = 7.6 Hz, Ph-C*H*H'-N), 4.61–4.50 (m, 2H, Ph-CH*H*'-N, O=C-C*H*-), 4.44 (dd, 1H, *J* = 5.8 Hz, *J* = 14.9 Hz, C*H*-CH_2-OH), 3.81 (dd, 1H, *J* = 4.7 Hz, *J* = 11.9 Hz, C*H*H'-OH), 3.64 (dd,

1H, *J* = 7.8 Hz, *J* = 11.9 Hz, CH*H*'-OH), 3.35 (bs, 1H, -O*H*), 1.49, 1.38 (2 × s, 3H each, 2 × -CH_3).

^{13}C-NMR ($CDCl_3$): δ 170.6 (*C*=O), 137.5, 128.9, 127.8, 127.6 (Ar), 110.1 (*C*Me_2), 77.7, 76.9 (2 × O-*C*H-), 61.7, 43.1 (-*C*H_2-OH, Ph-*C*H_2-), 27.0, 24.5 (2 × -*C*H_3).

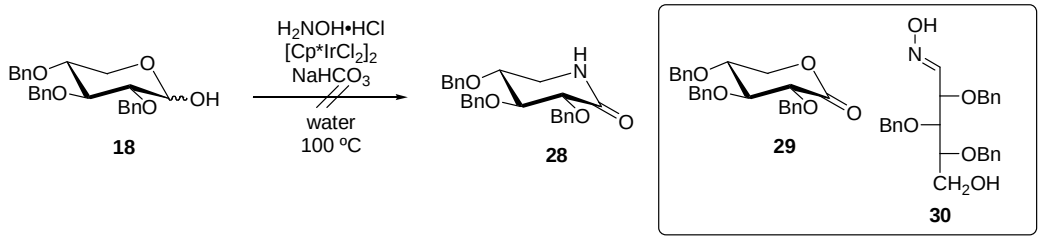


Attempted synthesis of (*3S,4R,5R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) pyrrolidin-2-one (25a).

The lactone **15** (117 mg; 0.28 mmol) was dissolved in MeOH (3 mL) and cooled to 0 °C. Ammonia (24 %, aq.; 1 mL) was then added and the solution was stirred for two hours. TLC (eluent: heptane/EtOAc 3:1), showed incomplete conversion, and another 0.5 mL of aq. ammonia was added. After one more hour, no further change was observed by TLC and the solution was concentrated *in vacuo*. A sample of the residue was analyzed by IR and characteristic primary amide and O-H bands were observed (3468, 3350 and 1671 cm^{-1}). The residue was then dissolved in PhMe (1 mL) and transferred to a heavy walled flask and $[Cp^*IrCl_2]_2$ (8 mg; 0.01 mmol) and $NaHCO_3$ (3 mg; 0.04 mmol) were added. The flask was sealed, and heated to 110 °C overnight. The solvent was removed, and the residue was purified by column chromatography (eluent: heptane/EtOAc 3:1). The desired lactam (**25a**) was not isolated. Instead lactone (**15**; 40 mg; 0.096 mmol; 34 %) was recovered as well as a new compound, probably **27** (35 mg, 0.11 mmol; 40 %):

^{1}H NMR ($CDCl_3$): δ 7.34–7.18 (m, 10H, Ar), 6.01 (d, 1H, *J* = 2.0 Hz, H-3), 4.99–4.94 (m, 2H, H-4, PhC*H*H'O-), 4.90 (d, 1H, *J* = 11.9 Hz, PhCH*H'*O-), 4.51 (d, 1H, *J* = 12.0 Hz, PhC*H'*HO-), 4.45 (d, 1H, *J* = 12.0 Hz, PhCH*H'*O-), 3.56 (dd, 1H, *J* = 3.5 Hz, *J* = 8.6 Hz, H-5), 3.52 (dd, 1H, *J* = 3.2 Hz, *J* = 8.6Hz, H-5').

^{13}C NMR ($CDCl_3$) δ 167.5 (*C*=O), 146.6 (C=*C*-OBn), 137.5, 134.8, 128.8, 128.7, 128.6, 127.9, 127.8 (Ar), 115.5 (*C*=C-OBn), 77.8, 73.8, 73.0, 70.7 (2 × Ph*C*H_2O, C-4, C-5).



Attempted synthesis of (3*S*,4*S*,5*R*)-3,4,5-tris(benzyloxy)piperidin-2-one (28)

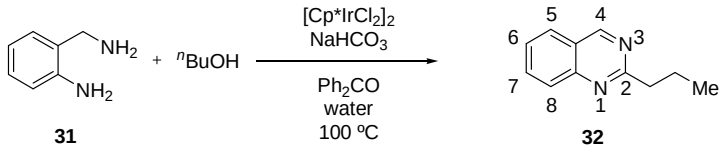
2,3,4-Tri-*O*-benzyl-D-xylopyranose (30 mg, 0.07 mmol), hydroxylamine hydrochloride (30 mg, 0.43 mmol), $[Cp^*IrCl_2]_2$ (8 mg, 10 μmol), and $NaHCO_3$ (10 mg, 0.12 mmol) were weighted into a heavy-walled flask and water (1 mL) was added. The flask was then purged with argon, sealed and heated to 100 °C overnight. After cooling to r.t. the reaction mixture was extracted with CH_2Cl_2 and the combined organic phases were concentrated and the residue purified by column chromatography (eluent: heptane/EtOAc 8:1). Major product was lactone **29** (10 mg, 0.024 mmol, 37 %).

IR: 3028, 2913, 2868, 1751, 1496, 1451, 1351, 1256.

^{13}C NMR ($CDCl_3$): δ 169.9, (*C*=O), 137.4, 137.4, 137.2, 128.7, 128.6, 128.4, 128.2, 128.1, 127.9 (Ar), 81.4, 78.2, 75.2, 73.4, 72.9, 70.6, 65.8 (C-2, C-3, C-4, C-5, 3 × Ph-*C*H_2-O).

When excess base was used the major product was oxime **30** (20 mg, 0.05 mmol, 52 %).

^{13}C NMR ($CDCl_3$) δ 149.9 (*C*=O), 138.1, 137.8, 137.3, 128.6, 128.4, 128.1, 128.1, 128.0, (Ar), 80.1, 79.3, 76.3, 74.8, 73.1, 71.4, 61.4 (3 × Ph-*C*H_2-O, C-2, C-3, C-4, C-5).

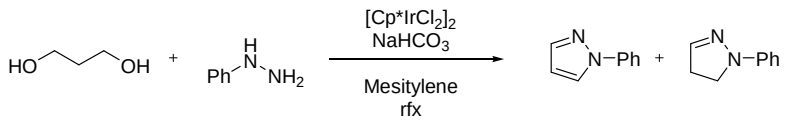


2-Propylquinazoline (32)

Same procedure as for the piperazine synthesis. Yield: 17 %.

^{1}H NMR ($CDCl_3$): δ 9.33 (s, 1H, H-4), 7.98–7.93 (m, 1H, H-8), 7.90–7.80 (m, 2H, H-5, H-7), 7.57 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.0 Hz, *J* = 8.1 Hz, H-6), 3.11-3.04 (m, 2H, Ar-C*H*$_2$-CH_2), 1.93 (tq, 1H, *J* = 5.4 Hz, *J* = 7.4 Hz, -C*H*$_2$-CH_3), 1.02 (t, 1H, *J* = 7.4Hz, -CH_3).

MS: *m/z* 172 [M].



Attempted synthesis of 1-phenylpyrazole

$[Cp^*IrCl_2]_2$ (48 mg, 0.060 mmol) was added to a flask followed by phenylhydrazine (1.3 g, 12 mmol), 1,3-propanediol (0.91 g, 12 mmol), and $NaHCO_3$ (23 mg, 0.27 mmol). The flask was flushed with argon and a condenser with a drying tube was attached. The mixture was then heated to 160 °C. After two hours GC-MS analysis showed moderate conversion into a mixture of compounds. The reaction was then allowed to proceed overnight, and was then cooled, diluted with aq. K_2CO_3 and CH_2Cl_2. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were concentrated and the residue was purified by column chromatography (eluent: CH_2Cl_2). 660 mg of a red oil was obtained and NMR analysis showed that was a 1:10 mixture of the 4,5-dihydropyrazole and the pyrazole (combined yield ~38 %). Separation was attempted by kugelrohr distillation and the 4,5-dihydropyrazole was obtained in acceptable purity. The fraction containing the pyrazole, however, was still contaminated.

4,5-Dihydro-1-phenyl-pyrazole:

^{1}H NMR ($CDCl_3$): δ 7.34–7.22 (m, 2H, N=C*H*-, Ar), 7.10–6.96 (m, 2H, Ar), 6.90–6.82 (m, 2H, Ar), 3.66 (t, 2H, *J* = 10.4 Hz, Ph-N-CH_2-),), 2.92 (dt, 2H, *J* = 1.8 Hz, *J* = 10.3 Hz, N=C-CH_2-).

^{13}C NMR ($CDCl_3$) δ 146.5 (*C*=N), 141.2 (N-C_{ipso}), 129.2, 119.3, 113.1 (Ar), 46.7 (Ph-N-*C*H_2-), 33.6 (N=C-*C*H_2-).

MS: *m/z* 135 [M+H].

6.1.1.3 Ligands and Ir-complexes

$[Cp^*IrCl_2]_2$

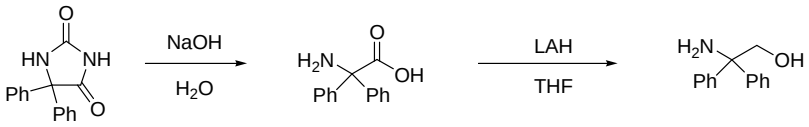
$IrCl_3$ hydrate (2.0 g, 6.7 mmol) was added to degassed MeOH (50 mL) in a Schlenk flask under Ar atmosphere. Cp*H (1.5 mL, 1.34 g, 9.58 mmol) was then added to the purple solution and the color changed to brown-gray. The mixture was heated to reflux temperature and stirred for 42 h. At this point the color had changed to deep-orange.

After cooling to r.t. the product was collected by filtration (Schlenk-technique) and washed with cold, degassed MeOH. The liquid from the filtration was cooled and more product precipitated and was collected. Combined yield: 1.64 g (2.06 mmol, 61 %).

^{1}H NMR ($CDCl_3$): δ 1.58 (s, 15H, -CH_3).

^{13}C NMR ($CDCl_3$) δ 86.4 (($C_5(CH_3)_5$), 9.5 ($C_5(CH_3)_5$).

For the procedure and NMR, see reference 131.



2-Amino-2,2-diphenylethanol

5,5-Diphenylhydantoin (9.3 g, 37 mmol) was added to an autoclave containing aqueous NaOH (20 %, 30 mL). The autoclave was then closed and heated to 185 °C in an oil bath. After 24 h the autoclave was allowed to cool to r.t. before it was opened. The reaction mixture was diluted with water (300 mL) and filtered. The filtrate was acidified with glacial acetic acid but no precipitate formed, even after one night at 5 °C. The mixture was then concentrated to dryness *in vacuo* and suspended in a minimum of water and filtered. The solid was analyzed by NMR and found to be the desired amino acid (with a small residue of acetic acid).

^{1}H NMR (DMSO-d_6): δ 7.48–7.19 (m, 10H, Ar), 1.84 (d, 2H, -NH_2).

^{13}C NMR (DMSO-d_6): δ 170.2 (*C*=O), 143.3, 128.1, 127.3, 126.6 (Ar), 69.0 (H_2N-*C*$(Ph)_2$).

Literature procedure: see ref. 148; for NMR data see ref. 149.

The crude amino acid was used for the next reaction without further purification:

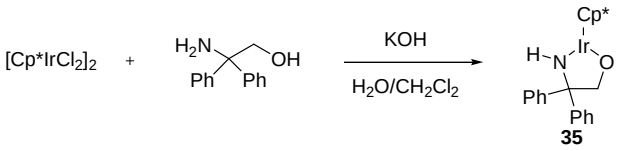
To a flask was added the LAH suspension (~1 M in THF; 16.5 mL, 16.5 mmol) and, the suspension was then cooled to 0 °C before the amino acid was added. The mixture was heated to reflux temperature and stirring continued for 4 hours. After cooling to r.t. water and sat. aq. NaOH was added carefully until no more gas evolution was observed. The reaction mixture was then transferred to a separatory funnel and diluted with CH_2Cl_2 and sat. aq. K_2CO_3. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic phases were dried (K_2CO_3) and

concentrated. This yielded the desired ethanolamine as a white solid (385 mg, 1.8 mmol, 19 %)

^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 10H, Ar), 4.11 (s, 2H –C*H*$_2$OH), 2.21 (bs, 3H, -N*H*$_2$; -O*H*).

^{13}C NMR ($CDCl_3$): δ 145.9, 128.5, 127.1, 126.9 (Ar), 70.2 (-*C*H$_2$-OH), 62.6 (H$_2$N-*C*(Ph)$_2$).

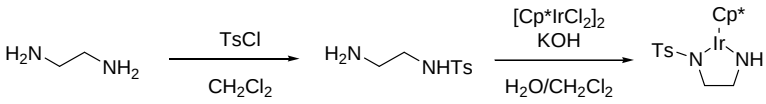
Literature procedure: see ref. 150.



Cp*Ir[κ^2(*N*,*O*)-OCH$_2$C(Ph)$_2$NH] (35)

To a solution of $[Cp^*IrCl_2]_2$ (100 mg, 0.13 mmol) and 2-amino-2,2-diphenylethanol (53 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) was added a solution of KOH (193 mg, 3.4 mmol) in water (2.5 mL; degassed). The mixture was stirred for 30 min. before the water was removed, and the organic phase was washed with water (2.5 mL), and dried over CaH_2. Evaporation of the solvent yielded the desired complex as a deep purple solid. The product was used directly without further purification.

Literature procedure: see ref. 151.



Cp*Ir[κ^2(*N*,*N*)-(HNCH$_2$CH$_2$NTs] (36)

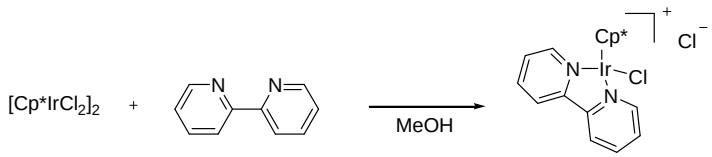
A solution of *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) in dichloromethane (25 mL) was slowly added to a stirred mixture of ethylenediamine (6.0 g, 100 mmol; 6.7 mL) in dichloromethane (25 mL). The resulting mixture was stirred for another 15 min, washed twice with water (25 mL) and dried over CaH_2 and filtered. The solvent was removed *in vacuo* to give a fine white powder (1.16 g; 5.4 mmol; 54 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* = 8.3 Hz, Ar), 7.31 (d, 2H, *J* = 8.5 Hz, Ar), 2.95 (dd, 1H, *J* = 4.6 Hz, *J* = 6.7 Hz, N-C*H*$_2$-), 2.78 (dd, 1H, *J* = 4.7 Hz, *J* = 6.5 Hz, N-C*H*$_2$-), 2.42 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 143.5, 137.0, 129.8, 127.2 (Ar), 45.5, 41.0 (2 × N-*C*H_2-), 21.6 (Ar-*C*H_3).

Literature procedure: see ref. 152.

$[Cp^*IrCl_2]_2$ (100 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (2.5 mL; degassed), and the diamine (54 mg, 0.25 mmol) was added. Then KOH (200 mg, 3.6 mmol dissolved in 2.5 mL water) was added, and the mixture was stirred vigorously at r.t. for 1 hour. The phases were then separated, and the organic phase was washed with water (2 × 3 mL). The organic phase was then dried (CaH_2) and concentrated to give a deep purple solid. TLC (eluent: CH_2Cl_2/THF 9:1) and NMR showed some byproduct, but further purification was not attempted. Yield: 100 mg; 0.19 mmol; 74 %.



39

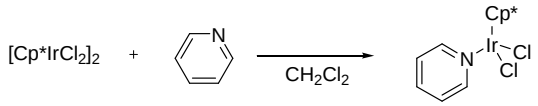
[Cp*Ir(bpy)Cl]Cl (39)

$[Cp^*IrCl_2]_2$ (114 mg, 0.14 mmol) was suspended in MeOH (40 mL), and 2,2'-bipyridine (45 mg, 0.29 mmol) was then added. Within two min. the solution had changed color to bright yellow, but some orange solid remained. The reaction mixture was stirred for an additional 60 min, and the last of the orange solids had disappeared. Some white precipitate had formed. This precipitate was filtered off, and the solution was concentrated dryness. The resulting solid was washed with heptane, and then dried *in vacuo* yielding 130 mg (0.23 mmol; 84 %).

^{1}H-NMR ($CDCl_3$): δ 9.33 (m, 2H, Ar) 8.80 (m, 2H, Ar), 8.27–8.26 (m, 2H, Ar), 7.78–7.77 (m, 2H, Ar), 1.71–1.69 (m, 15, -C*H*$_3$).

^{1}H-NMR (D_2O): δ 8.91 (ddd, 2H, *J* = 0.6 Hz, *J* = 1.4 Hz, *J* = 5.6 Hz), 8.44 (dd, 2H, *J* = 0.5 Hz, *J* = 8.3 Hz), 8.18 (dt, 2H, *J* = 1.5 Hz, *J* = 8.0 Hz), 7.75 (ddd, 2H, *J* = 1.3 Hz, *J* = 5.6 Hz, *J* = 7.6 Hz), 1.60 (s, 15H).

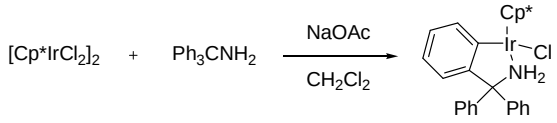
The NMR samples were kept standing for two weeks, and new spectra were recorded. Only small changes were observed, and it seems that the complex is quite stable in solution (both D_2O and $CDCl_3$).



40

Cp*Ir(Pyr)Cl$_2$ (40)

[Cp*IrCl$_2$]$_2$ (100 mg, 0.13 mmol) was suspended in pyridine (2 mL), and a little CH_2Cl_2 (~0.5 mL) was added. After 5 min the mixture was concentrated *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 8.98–8.95 (m, 2H, Pyr-H2, Pyr-H6), 7.74 (tt, 1H, *J* = 1.5 Hz, *J* = 7.7 Hz, Pyr-H4), 7.35 (ddd, 2H, *J* = 1.4 Hz, *J* = 5.3 Hz, *J* = 7.6 Hz), 1.53 (s, 15H, Cp*).



41

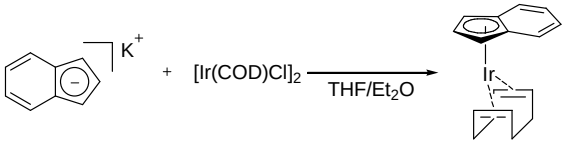
Cp*IrCl[κ^2(*N*,*C*)-(NH$_2$C(Ph)$_2$-2-C$_6$H$_4$)] (41)

[Cp*IrCl$_2$]$_2$ (20 mg, 0.025 mmol), NaOAc (5 mg, 0.06 mmol) and tritylamine (13 mg, 0.05 mmol) were weighed into a Schlenk tube and vacuum was applied. The tube was then filled with Ar (repeated twice). CH_2Cl_2 (1 mL) was added and the resulting solution was stirred at r.t. for 20 h. The solvent was removed *in vacuo* and the resulting solid was taken up in PhMe and filtered. Concentration to dryness gave the desired product.

^{1}H NMR ($CDCl_3$): δ 7.60 (dd, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz, Ar), 7.40–7.34 (m, 2H, Ar), 7.28–7.08 (m, 8H, Ar), 7.05 (dd, 1H, *J* = 1.4 Hz, *J* = 7.4 Hz, Ar), 6.76 (dt, 1H, *J* = 1.3 Hz, *J* = 7.4 Hz, Ar), 6.25 (dd, 1H, *J* = 1.3 Hz, *J* = 7.5 Hz, Ar), 5.72 (d, 1H, *J* = 10.8 Hz, N*H*H'), 4.97 (d, 1H, *J* = 10.5 Hz, NH*H'*), 1.41 (s, 15H, Cp*).

For the procedure and NMR, see ref. 63.

^{13}C NMR ($CDCl_3$): δ 157.0, 152.7, 147.6, 144.5, 136.5, 129.1, 129.0, 128.6, 128.4, 128.3, 127.5, 127.5, 126.7, 125.4, 122.1 (Ar), 86.9 ($C_5(CH_3)_5$), 80.1 (H_2N-$C(Ph)_2$-C_6H_4), 8.9 ($C_5(CH_3)_5$).

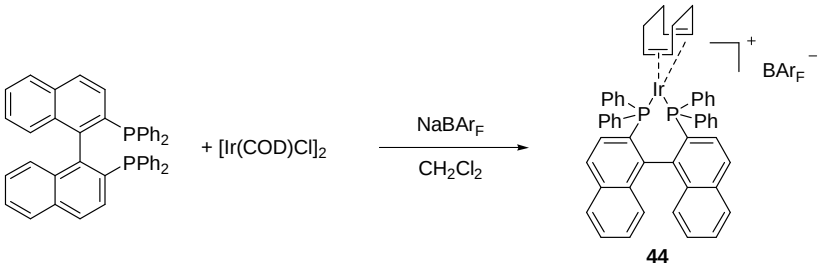


(η^5-Indenyl)(COD)Ir (43)

Potassium indenide was prepared by adding KH (24 mg, 0.60 mmol) to a solution of indene (70 mg, 0.60 mmol) in THF (30 mL) and stirring for 1 hour at r.t. Half of the potassium indenide solution was then transferred to another Schlenk flask containing $[Ir(COD)Cl]_2$ (80 mg, 0.12 mmol) in ether (70 mL) at 0 °C. The resulting dark purple solution was stirred for 4 hours. After removal of the solvent, it was attempted to precipitate the product by addition of pentane, but this was unsuccessful. Purification was achieved by loading the crude mixture onto neutral aluminium oxide and eluting with ether. The yellow fractions were collected and concentrated. The resulting solid was recrystallized (pentane; freezer; several days) to give the desired product as purple needle like crystals in 38 % yield (19 mg; 0.046 mmol). The impurity was mainly COD (identified by NMR) and the complex was used without further purification.

^{1}H NMR ($CDCl_3$): δ 7.24–7.18 (m, 2H), 7.00–7.05 (m, 2H), 5.91 (t, 1H, *J* = 2.5 Hz, H-2), 5.24 (d, 2H, *J* = 2.5 Hz, H-1, H-3), 3.82-3.75 (m, 8H, COD C*H*$_2$).

^{13}C NMR ($CDCl_3$): δ 123.6, 120.6 (Ph), 109.8 (C-8, C-9), 84.1 (C-2), 71.5 (C-1, C-3), 50.2 (COD-*C*H), 33.0 (COD *C*H$_2$).[64b]



44

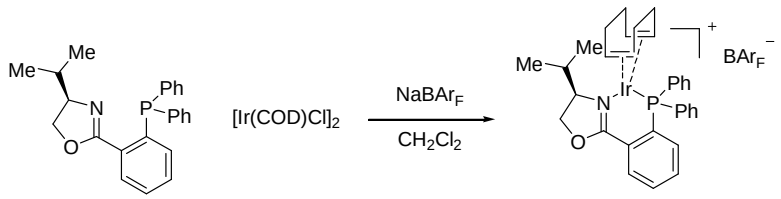
((±)-BINAP)(COD)iridium(I) BAr_F (44)

Into a Schlenk tube were weighed $[Ir(COD)Cl]_2$ (10 mg, 0.015 mmol) and (±)-BINAP (19 mg, 0.030 mmol). Vacuum was then applied and the flask was back-filled with Ar (repeat twice). CH_2Cl_2 (0.5 mL, dry, degassed) was added and the resulting suspension was added to a suspension of $NaBAr_F$ in CH_2Cl_2 under Ar. The mixture was stirred for 1 hour and then filtered through $MgSO_4$. Heptane was added and the volume reduced to 2 mL which caused precipitation. The liquid phase was removed by pipette and the residue

was washed with pentane. Further purification was achieved by column chromatography (eluent: CH_2Cl_2) and the title compound was obtained as a purple solid (47 mg, 0.026 mmol, 88 %).

^{1}H NMR ($CDCl_3$): δ 7.86–7.46 (m, 28H, Ar), 7.35 (ddd, 2H, *J* = 1.0 Hz, *J* = 6.9 Hz, *J* = 8.1 Hz, Ar), 7.25–7.17 (m, 4H, Ar), 7.01 (ddd, 2H, *J* = 1.2 Hz, *J* = 6.8 Hz, *J* = 8.3 Hz, Ar), 6.80–6.74 (m, 2H, Ar), 6.75 (m, 1H), 6.63 (t, 4H, *J* = 7.1 Hz, Ar), 6.44, (d, 2H, *J* = 8.6 Hz, Ar), 4.46 (dt, 2H, *J* = 3.0 Hz, *J* = 7.1 Hz, COD C=C*H*), 4.17 (dd, 2H, *J* = 7.5 Hz, *J* = 12.6 Hz, COD C=C*H*), 2.40–2.14 (m, 4H, COD), 2.14–1.98 (m, 2H, COD CH_2), 1.90–1.78 (m, 2H, COD CH_2).

^{13}C NMR ($CDCl_3$): δ 134.9, 134.6, 134.1, 133.8, 131.7, 130.4, 129.2, 128.8, 128.8, 128.1, 127.9, 127.2, 126.5 (Ar), 122.9, 117.6 (COD *C*=*C*), 32.6, 29.4 (COD-*C*H_2).



45

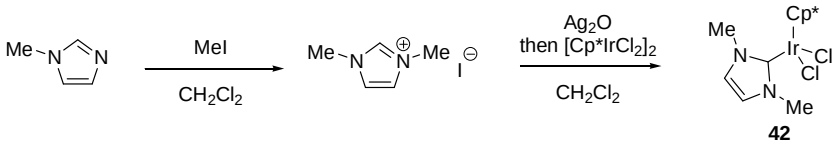
(4*R*)-2-(2-Diphenylphosphanylphenyl)-4-isopropyl-4,5-dihydrooxazole-(COD)iridium(I) tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (45)

A heavy walled flask was charged with $[Ir(COD)Cl]_2$ (10 mg, 0.015 mmol), the PHOX ligand (11.4 mg, 0.030 mmol) and then purged with Ar. CH_2Cl_2 (1 mL, dry, degassed) was added and the flask was sealed, and heated to 50 °C for 90 min. The flask was cooled to r.t. and the red solution was added to a suspension of $NaBAr_F$ (56 mg, 0.63 mmol) in water (4 mL) and the mixture was stirred vigorously for 1 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (eluent: CH_2Cl_2) and the title compound was obtained (27 mg, 0.018 mmol, 60 %).

^{1}H NMR ($CDCl_3$): δ 8.15–8.08 (m, 1H, Ar), 7.76–7.36 (m, 23H, Ar), 7.08 (m, 2H, Ar), 5.04–4.85 (m, 2H, 2 × COD-C*H*), 4.42 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, O-C*H*H'-C(^{i}Pr)), 4.33 (t, 1H, *J* = 9.4 Hz, O-CH*H'*-C(^{i}Pr)), 4.14–4.08 (m, 1H, COD C=C*H*), 3.36–3.27 (m,

1H, C=C*H*), 3.10–3.00 (m, 1H, C=C*H*), 2.66–2.34 (m, 4H, C=C*H*, 3 × COD C*H*H), 2.15–1.90 (m, 2H, 2 × COD C*H*H), 1.75–1.36 (m, 4H, C*H*(CH_3)$_2$, 3 × COD C*H*H), 0.82 (d, 3H, *J* = 7.1 Hz, -CH_3), -0.11 (d, 3H, *J* = 6.7 Hz, -CH_3).

^{13}C NMR ($CDCl_3$): δ 169.0, 161.6, 135.0, 133.4, 133.3, 132.4, 130.1, 130.0, 129.2, 128.9, 128.9, 126.6, 122.9, 117.7 (N=*C*, Ar), 97.3, 93.7 (2 × COD), 70.7, 68.5, 64.2, 63.6 (2 × COD, O-*C*H_2-C^{i}Pr, CH_2-*C*^{i}Pr), 36.4, 33.1, 32.4, 28.7, 26.7, (4 × COD, *C*H(CH_3)$_2$), 18.8 (-*C*H_3), 12.5 (-*C*H_3).[66]



42

Cp*Ir(IMe)Cl$_2$

To a solution of 1-methylimidazole (4.10 g, 50 mmol, 4.0 mL) in CH_2Cl_2 (10 mL) at 0 °C was added MeI (7.15 g, 50 mmol, 3.14 mL, in 5 mL CH_2Cl_2) over 30 min. The ice bath was removed and stirring continued at r.t. for 30 min. Removal of the volatiles under reduced pressure gave *N*,*N*'-dimethylimidazolium iodide as a white solid. Yield: 10.4 g, 46 mmol, 92 %.

^{1}H NMR (DMSO-d_6): δ 9.06 (s, 1H, H-2), 7.69 (s, 2H, H-4, H-5), 3.85 (s, 6H, 2 × N-CH_3).

^{13}C NMR (DMSO-d_6): δ 136.9 (C-2), 123.3 (C-4, C-5), 35.7 (2 × N-*C*H_3).

N,*N*'-Dimethylimidazolium iodide (42 mg, 0.19 mmol) was dissolved in CH_2Cl_2 in a Schlenk tube under N_2. Silver oxide (37 mg, 0.16 mmol) was then added and a white precipitate formed immediately. The suspension was stirred for 30 min. before [Cp*IrCl_2]$_2$ (75 mg, 0.094 mmol) was added. The resulting orange mixture was stirred for four hours while being monitored by TLC (eluent: CH_2Cl_2/THF 9:1). When all [Cp*IrCl_2]$_2$ was consumed, the mixture was filtered through a bed of silica, which was then washed with CH_2Cl_2/THF (9:1) until the eluent was colourless. Removal of the solvent yielded **42** as a yellow solid (73 mg, 0.15 mmol, 79 %).

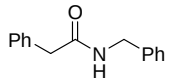
^{1}H NMR ($CDCl_3$): δ 6.91 (s, 2H, N-C*H*=C*H*-N), 3.94 (s, 6H, 2 × N-CH_3), 1.61 (s, 15H, Cp*).

^{13}C NMR ($CDCl_3$): δ 156.2 (N-*C*-Ir), 123.3 (N-*C*H=*C*H-N), 88.7 ($C_5(CH_3)_5$), 38.7 (2 × N-*C*H_3), 9.3 ($C_5(CH_3)_5$).

6.1.2 Ruthenium catalyzed preparation of amides from alcohols and amines by extrusion of dihydrogen

6.1.2.1 General procedure for the amidation of alcohols and amines

$Ru(COD)Cl_2$ (7.0 mg, 0.025 mmol), $PCyp_3 \cdot HBF_4$ (8.2 mg, 0.025 mmol), 1,3-diisopropylimidazolium chloride (4.7 mg, 0.025 mmol), and ^{t}BuOK (11.2 mg, 0.10 mmol) were weighted into an oven-dried Schlenk tube. A condenser was attached and vacuum applied before the flask was filled with argon (repeat twice). Freshly distilled toluene (1 mL) was then added and the mixture was heated to reflux temperature for 20 min. The flask was removed from the oil bath and the alcohol (0.5 mmol) and amine (0.5 mmol) were added. The flask was returned to the oil bath for 24 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was purified by column chromatography (eluent: pentane/EtOAc 4:1 → 1:1) to give the amide.



_N_-Benzyl-2-phenylacetamide

Catalyst loading: 2 mol%.

Isolated yield: 93 %.

White solid.

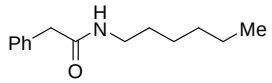
IR (KBr): 3288, 3063, 3030, 1637, 1551, 1454, 1431, 1029, 693, 602.

Mp. 118–119 °C. Lit[153]: 118–119 ºC.

^{1}H NMR ($CDCl_3$): δ 7.38–7.15 (m, 10H, Ar), 5.88 (bs, 1H, -CON*H*-), 4.40 (d, 2H, *J* = 5.8 Hz, N-CH_2-Ph), 3.61 (s, 2H, Ph-CH_2-CO).[154]

^{13}C NMR ($CDCl_3$): δ 171.0 (*C*=O), 138.2, 134.9, 129.5, 129.1, 128.7, 127.6, 127.5, 127.5 (Ar), 43.9, 43.6 (2 × -*C*H_2-).

MS: *m/z* 226 [M+H].



_N_-Hexyl-2-phenylacetamide

Catalyst loading: 2 mol%.

Isolated yield: quant.

White solid.

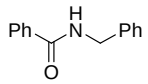
IR (KBr): 3254, 3066, 2937, 1628, 1552, 1477, 1156, 692, 544.

Mp. 55–57 °C. Lit[155]: 53–54 ºC.

^{1}H NMR ($CDCl_3$): δ 7.33–7.18 (m, 5H, Ar), 6.13 (bs, 1H, -CON*H*-), 3.48 (s, 2H, Ph-CH_2-N), 3.18–3.09 (m, 2H, N-CH_2-CH_2-), 1.38 (p, 2H, *J* = 7.0 Hz, N-CH_2-CH_2-), 1.26–1.13 (m, 6H, 3 × -CH_2-), 0.82 (t, 1H, *J* = 6.7 Hz, -CH_3).

^{13}C NMR ($CDCl_3$): δ 171.0 (*C*=O), 135.3, 129.2, 128.7, 127.0 (Ar), 43.6 (Ph-*C*H_2-N), 39.6 (N-*C*H_2-CH_2-), 31.3, 29.3, 26.4, 22.4 (4 × -*C*H_2-), 13.9 (-*C*H_3).[156]

MS: *m/z* 219 [M].



_N_-Benzylbenzamide

Catalyst loading: 5 mol%.

Isolated yield: 78 %.

White solid.

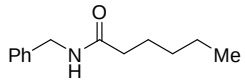
IR (neat): 3322, 1642, 1543, 1418, 1313, 1260, 728, 693.

Mp. 98–100 °C (recryst. from H_2O/EtOH). Lit[157]: 104 °C.

^{1}H NMR ($CDCl_3$): δ 7.82–7.77 (m, 2H, Ar), 7.55–7.25 (m, 8H, Ar), 6.54 (bs, 1H, -CON*H*-), 4.64 (d, 2H, *J* = 5.7 Hz, N-CH_2-Ph).

^{13}C NMR ($CDCl_3$): δ 167.5 (*C*=O), 138.3, 134.5, 131.7, 128.9, 128.7, 128.0, 127.7, 127.1, (Ar), 44.2 (N-*C*H_2-Ph).[157]

MS: *m/z* 211 [M].



_N_-Benzylhexanamide

Catalyst loading: 5 mol%.

Isolated yield: 60 %.

Colorless crystals.

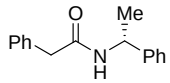
IR ($CHCl_3$): 3291, 3085, 2957, 2928, 1639, 1552.1454, 697.

Mp. 50–52 °C (recryst. from pentane). Lit[158]: 52–53.5 °C.

^{1}H NMR ($CDCl_3$): δ 7.37–7.25 (m, 5H, Ar), 5.69 (bs, 1H, CON-*H*), 4.45 (d, 2H, *J* = 5.7 Hz, N-C*H*$_2$-Ph), 2.21 (t, 2H, *J* = 7.4 Hz, -C*H*$_2$-C=O), 1.66 (p, 2H, *J* = 7.5 Hz, -C*H*$_2$-CH$_2$-C=O), 1.37–1.24 (m, 4H, CH$_3$-C*H*$_2$-C*H*$_2$-), 0.89 (t, 3H, *J* = 6.8 Hz, -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 173.2 (*C*=O), 138.5, 128.8, 127.9, 127.6 (Ar), 43.6 (N-*C*H$_2$-Ph), 36.9 (-*C*H$_2$-C=O, 31.6 (-*C*H$_2$-), 25.6 (-*C*H$_2$-), 22.5 (-*C*H$_2$-CH$_3$), 14.1 (-*C*H$_3$).

MS: *m/z* 205 [M].



2-Phenyl-*N*-((*R*)-1-phenylethyl)acetamide

Catalyst loading: 5 mol%.

Isolated yield: 70 %.

$[\alpha]_D$ +3.4 °(*c* = 1.0, $CHCl_3$). Ref[r]: $[\alpha]_D$ +3.3 °(*c* = 1.0, $CHCl_3$).

$[\alpha]_{436}$ +11.9 °(*c* = 1.0, $CHCl_3$). Ref: $[\alpha]_{436}$ +11.4 °(*c* = 1.0, $CHCl_3$).

IR (KBr): 3307, 3063, 3028, 2974, 1649, 1541, 1494, 1445, 1356, 1246, 1208, 761, 697.

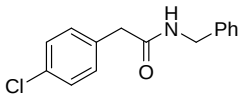
Mp. 115–116 °C (recryst. from H_2O/EtOH). Lit[159]: 117–118 ºC.

^{1}H NMR ($CDCl_3$): δ 7.39–7.61 (m, 10H, Ar), 5.72 (d, 1H, *J* = 7.1 Hz, -CON*H*-), 5.12 (p, 1H, *J* = 7.0 Hz, PhC*H*(Me)N-), 3.57 (s, 2H, Ph-C*H*$_2$-), 1.40 (d, 3H, *J* = 6.9 Hz, -C*H*$_3$).[159]

^{13}C NMR ($CDCl_3$): δ 170.1 (*C*=O), 143.2, 135.0, 129.5, 129.1, 128.7, 127.4, 127.4, 126.0 (Ar), 48.8 (Ph*C*H(Me)N-), 44.0 (Ph-*C*H$_2$-), 21.9 (-*C*H$_3$).

MS: *m/z* 239 [M].

[r] Prepared by acylation. *Vide infra*.



***N*-Benzyl-2-(4-chlorophenyl)acetamide**

Catalyst loading: 2 mol%.

Isolated yield: 83 %.

Colorless crystals.

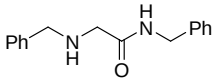
IR (neat/solid): 3277, 3026, 2917, 1642, 1539, 1491, 1246, 690.

Mp. 151–153 °C. Lit[160]: 155–156 °C.

^{1}H NMR (DMSO-*d6*): δ 8.58 (t, 1H, *J* = 5.7 Hz, -CON*H*-), 7.39–7.20 (m, 9H, Ar), 4.27 (d, 2H, *J* = 5.9 Hz, N-C*H*$_2$-Ph), 3.49 (s, 2H, Ar-C*H*$_2$-CO).

^{13}C NMR (DMSO-*d6*): δ 169.7 (*C*=O), 139.3, 135.3, 131.0, 130.8, 128.2, 128.1, 127.2, 126.7 (Ar), 42.2, 41.4 (2 × -CH$_2$-).

MS: *m/z* 259 [M].



***N*-Benzyl-2-(benzylamino)acetamide**

Catalyst loading: 5 mol%.

Isolated yield: 90 %.

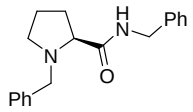
Clear oil.

IR (neat): 3319, 3029, 1654, 1522, 1453, 1261, 1029, 737, 699.

^{1}H NMR ($CDCl_3$): δ 7.53 (bs, 1H, -CON*H*-), 7.40–7.20 (m, 10H, Ar), 4.47 (d, 2H, *J* = 6.0 Hz, Ph-C*H*$_2$-NC(=O)), 3.76 (s, 2H, Ph-C*H*$_2$-NH-CH$_2$-), 3.36 (s, 2H, Ph-CH$_2$-NH-C*H*$_2$-), 1.80 (bs, 1H, -CH$_2$-N*H*-CH$_2$).

^{13}C NMR ($CDCl_3$): δ 171.5 (*C*=O), 139.4, 138.5, 128.8, 128.7, 128.2, 127.8, 127.6, 127.5 (Ar), 54.1, 52.1 (2 × -*C*H$_2$-), 43.1 (Ph-*C*H$_2$-NC(=O)).

MS: *m/z* 255 [M+H].



***N,N'*-Dibenzyl-L-prolinamide**

Catalyst loading: 5 mol%.

Isolated yield: 60 %.

Clear oil.

$[\alpha]_D$ -48.2 ° (*c* = 1.0, $CHCl_3$). Ref[s]: $[\alpha]_D$ -46.3 ° (*c* = 1.0, $CHCl_3$).

IR (neat): 3346, 3061, 2968, 2806, 1670, 1514, 1454, 1028, 748, 700.

^{1}H NMR ($CDCl_3$): δ 7.74 (bs, 1H, -CON*H*-), 7.22–7.37 (m, 8H, Ar), 7.17–7.11 (m, 2H, Ar), 4.41 (d, 2H, *J* = 5.7 Hz, Ph-CH_2-NC=O), 3.85 (d, 1H, *J* = 12.8 Hz, Ph-C*H*H'-N-), 3.48 (d, 1H, *J* = 12.8 Hz, Ph-CH*H*'-N-), 3.29 (dd, 1H, *J* = 4.9 Hz, *J* = 10.2 Hz, H-2), 3.00 (ddd, 1H, *J* = 2.2 Hz, *J* = 6.6 Hz, *J* = 8.9 Hz, H-5a), 2.20–2.41 (m, 2H, H-3a, H-5b), 1.95 (ddd, 1H, *J* = 4.0 Hz, *J* = 8.2 Hz, *J* = 13.0 Hz, H-3b), 1.84–1.61 (m, 2H, H-4a, H-4b).

^{13}C NMR ($CDCl_3$): δ 174.5 (*C*=O), 138.5, 138.5, 128.7, 128.7, 128.4, 127.6, 127.4, 127.3 (Ar), 67.3 (C-2), 60.0, 53.9 (C-5, Ph-*C*H_2-N), 42.9 (Ph-*C*H_2-NC=O), 30.7 (C-3), 24.2 (C-4).[161]

MS: *m/z* 295 [M+H].

2-Pyrrolidinone

Catalyst loading: 5 mol%.

Isolated yield: 65 %.

Colorless crystals.

IR (neat): 3247, 3198, 2921, 2867, 1679, 1462, 1283, 419.

Mp. 26–27 °C. Lit[162]: 25 °C.

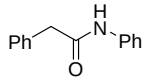
^{1}H NMR ($CDCl_3$): δ 6.50 (bs, 1H, -CON*H*-), 3.39 (t, 2H, *J* = 7.0 Hz, NH-CH_2-CH_2-), 2.35–2.25 (m, 2H, CO-CH_2-CH_2-), 2.20–2.05 (m, 2H, NH-CH_2-CH_2-).

[s] Compound prepared by HBTU mediated coupling between *N*-benzyl-L-proline and $BnNH_2$. *Vide infra*.

^{13}C NMR ($CDCl_3$): δ 179.3 (*C*=O), 42.4 (NH-*C*H_2-CH_2-), 30.1 (CO-*C*H_2-CH_2-), 20.9 (NH-CH_2-*C*H_2-).

For selected NMR shifts, see reference 163.

MS: *m/z* 85 [M].



***N*,2-Diphenylacetamide**

Catalyst loading: 5 mol%.

Isolated yield: 21 %.

Colorless crystals.

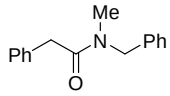
IR ($CHCl_3$): 3286, 3257, 3060, 1655, 1599, 1547, 1495, 1442, 1166, 751, 723, 692.

Mp. 114–115 °C (recryst. from heptane). Lit[164]: 115–116 °C.

^{1}H NMR ($CDCl_3$): δ 7.46–7.20 (m, 10H, Ar, CON-*H*), 7.12–7.05 (m, 1H, Ar), 3.73 (s, 2H, Ph-C*H*$_2$-C=O).[165]

^{13}C NMR ($CDCl_3$): δ 169.3 (*C*=O), 137.7, 134.5, 129.6, 129.3, 129.0, 127.8, 124.6, 119.9 (Ar), 44.9 (Ph-*C*H_2-C=O).

MS: *m/z* 211 [M].



***N*-Benzyl-*N*-methyl-2-phenylacetamide**

Catalyst loading: 5 mol%.

Isolated yield: 40 %.

Yellow oil.

IR ($CHCl_3$): 3061, 3029, 1644, 1495, 1453, 1399, 1111, 731, 697.

1:1.4 mixture of rotamers. Major rotamer:

^{1}H NMR ($CDCl_3$): δ 7.39–7.20 (m, 9H, Ar), 7.12–7.09 (m, 1H, Ar), 4.61 (s, 2H, N-C*H*$_2$-Ph), 3.78 (s, 2H, Ph-C*H*$_2$-C=O), 2.89 (s, 3H, N-C*H*$_3$).[166]

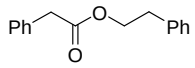
^{13}C NMR ($CDCl_3$): δ 171.2 (*C*=O), 137.4, 135.0, 128.9, 128.8, 128.6, 128.1, 126.9, 126.4 (Ar), 51.0 (N-*C*H_2-Ph), 41.3 (Ph-*C*H_2-C=O), 35.3 (N-*C*H_3).

Minor rotamer:

^{1}H NMR ($CDCl_3$): δ 7.39–7.20 (m, 9H, Ar), 7.09–7.07 (m, 1H, Ar), 4.52 (s, 2H, N-C*H*$_2$-Ph), 3.75 (s, 2H, Ph-C*H*$_2$-C=O), 2.95 (s, 3H, N-C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 171.6 (*C*=O), 136.5, 135.2, 129.0, 128.9, 128.8, 127.7, 127.4, 126.9 (Ar), 53.7 (N-*C*H$_2$-Ph), 41.0 (Ph-*C*H$_2$-C=O), 34.1 (N-*C*H$_3$).

MS: *m/z* 239 [M].



2-Phenylethyl 2-phenylacetate

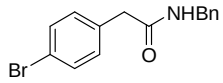
Clear oil.

IR (neat): 3029, 2957, 1730, 1496, 1454, 1245, 1138, 1000, 748, 723, 696.

^{1}H NMR ($CDCl_3$): δ 7.40–7.17 (m, 10H, Ar), 4.36 (t, 2H, *J* = 7.0 Hz, O-C*H*$_2$-CH$_2$-Ph), 3.65, (s, 2H, Ph-C*H*$_2$-C=O), 2.96 (t, 2H, *J* = 6.9 Hz, O-CH$_2$-C*H*$_2$-Ph).[167]

^{13}C NMR ($CDCl_3$): δ 171.8 (*C*=O), 138.0, 134.3, 129.6, 129.2, 128.8, 128.8, 127.3, 126.8 (Ar), 65.6 (O-*C*H$_2$-CH$_2$-Ph), 41.7 (Ph-*C*H$_2$-C=O), 35.3 (O-CH$_2$-*C*H$_2$-Ph).

MS: *m/z* 240 [M].



***N*-benzyl-2-(4-bromophenyl)acetamide**

Catalyst loading: 5 mol%.

Isolated yield: 3 % (85 % alcohol recovered).

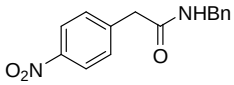
^{1}H NMR ($CDCl_3$): δ 7.50–7.13 (m, 9H, Ar), 5.67 (bs, 1H, N-*H*), 4.42 (d, 2H, *J* = 5.8 Hz, -C*H*$_2$-NH), 3.56 (s, 2H, Ph-C*H*$_2$-C=O).

MS: *m/z* 303 [M].

Amine by-product (10 %)

^{1}H NMR ($CDCl_3$): δ 7.44–7.05 (m, 9H, Ar), 3.80 (s, 2H, N-C*H*$_2$-Ph), 2.92–2.85 (m, 2H, Ph-CH$_2$-C*H*$_2$-), 2.81–2.73 (m, 2H, Ph-CH$_2$-C*H*$_2$-), 1.52 (bs, 1H, N-*H*).[168]

^{13}C NMR ($CDCl_3$): δ 140.2, 139.1, 131.6, 130.6, 128.5, 128.2, 127.1, 120.0 (Ar), 54.0 (N-*C*H$_2$-Ph), 50.4 (Ph-CH$_2$-*C*H$_2$-), 35.9 (Ph-*C*H$_2$-CH$_2$-).



_N_-benzyl-2-(4-nitrophenyl)acetamide

Catalyst loading: 5 mol%.

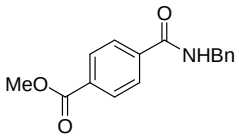
Isolated yield: 4 %.

Red solid.

^{1}H NMR ($CDCl_3$): δ 8.19 (d, 2H, *J* = 8.6 Hz, Ar), 7.46 (d, 2H, *J* = 8.8 Hz, Ar), 7.36–7.20 (m, 5H, Ar), 5.89 (bs, 1H, N-*H*), 4.43 (d, 2H, *J* = 5.7 Hz, -C*H*$_2$-NH), 3.67 (s, 2H, Ph-C*H*$_2$-C=O).

^{13}C NMR ($CDCl_3$): δ 159.0 (*C*=O), 137.8, 130.3, 128.9, 127.9, 127.9, 124.1 (Ar), 44.1, 43.4 (2 × -*C*H$_2$-).

MS: *m/z* 270 [M].



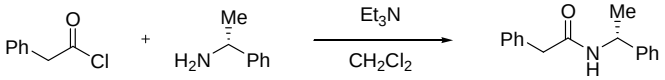
Methyl 4-(benzylcarbamoyl)benzoate

^{1}H NMR ($CDCl_3$): δ 8.06 (d, 2H, *J* = 8.4 Hz, Ar), 7.83 (d, 2H, *J* = 8.4 Hz, Ar), 7.45–7.25 (m, 5H, Ar), 6.65 (bs, 1H, N-*H*), 4.63 (d, 2H, *J* = 5.6 Hz, -C*H*$_2$-), 3.93 (s, 3H, -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 166.7, 166.4 (2 × *C*=O), 137.8, 130.3, 128.9, 127.9, 127.9, 124.1 (Ar), 44.1, 43.4 (-*C*H$_2$-, -O*C*H$_3$).

MS: *m/z* 269 [M].

6.1.2.2 Synthesis of reference materials and substrates

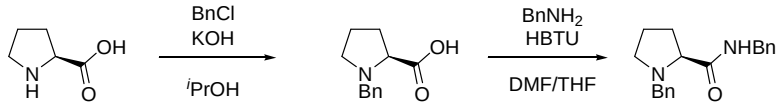


2-Phenyl-*N*-((*R*)-1-phenylethyl)acetamide

The acid chloride (928 mg, 0.79 mL, 6 mmol) was added to CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere. A solution of the amine (763 mg, 0.80 mL, 6.3 mmol) in Et_3N (1 mL) was added drop-wise. The reaction mixture was then stirred overnight while

slowly reaching room temperature. The mixture was then cooled back to 0 °C and diluted with CH_2Cl_2 (15 mL) before water (10 mL) was added. The phases were then separated and the organic phase was washed with 2 M H_2SO_4 (10 mL), sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated to give the amide (1.18 g, 4.9 mmol, 82 %). The residue was recrystallized from H_2O/EtOH. $[\alpha]_D$ +3.3 °(*c* = 1.0, $CHCl_3$). $[\alpha]_{436}$ +11.4 °(*c* = 1.0, $CHCl_3$).

NMR spectra were identical to those obtained by the Ru-catalyzed reaction (*vide supra*).



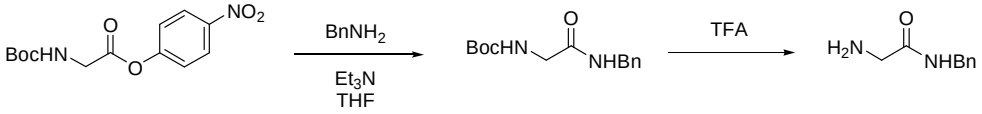
***N,N'*-Dibenzyl-L-prolinamide**

L-Proline (0.50 g, 4.34 mmol) and KOH (0.73 g, 13 mmol) were added to a flask followed by ^{i}PrOH (5 mL). The mixture was heated to 40 °C and when a clear solution was obtained the BnCl (0.59 g, 0.53 mL, 4.6 mmol) was added drop-wise over 2 hours. After the addition was complete the reaction mixture was stirred for 6 hours and then cooled to room temperature. pH was adjusted to 4–5 by conc. HCl. Chloroform (10 mL) was added and the mixture was stirred overnight. The precipitate was removed by filtration and was washed with CH_2Cl_2. The mother liquor and the washings were combined and concentrated to give a solid residue which was washed with acetone to give *N*-benzyl-L-proline (877 mg, 4.27 mmol, 98 %). The crude product was used directly for the next reaction.

The acid from the previous reaction was dissolved in DMF/THF (5:2; 35 mL) and $BnNH_2$ (460 mg, 0.47 mL, 4.3 mmol) was added followed by K_2CO_3 (1.78 g, 12.9 mmol) and HBTU (1.63 g, 4.3 mmol). The mixture was stirred for 3 hours at r.t. and then quenched by water (30 mL). The mixture was then extracted with EtOAc (2 × 40 mL) and the combined organic phases were washed with 1 % aq. $NaHCO_3$ (5 × 40 mL), brine (40 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (eluent: pentane/EtOAc 4:1 → 1:1). The desired product was obtained as a clear oil in 57 % yield (2 steps, 725 mg, 2.46 mmol).

$[\alpha]_D$ -46.3 ° (*c* = 1.0, $CHCl_3$).

NMR spectra were identical to those obtained by the Ru-catalyzed reaction (*vide supra*). This procedure has been described in the literature.[169]



***N*-Benzylglycinamide**

The activated glycine ester (475 mg, 1.60 mmol) was dissolved in dry THF (10 mL) under argon and $BnNH_2$ (171 mg, 174 µL, 1.60 mmol). The color changed immediately to yellow. Et_3N (0.97 g, 0.73 mL, 9.6 mmol) was added and the reaction mixture was stirred for 2 hours. TLC analysis (eluent: pentane/EtOAc 1:1) showed complete conversion and the mixture was concentrated *in vacuo*. The residue was taken up in EtOAc (20 mL) and washed with 1 M HCl (10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. After column chromatography (eluent: pentane/EtOAc 1:1) the amide was obtained as a clear syrup (341 mg, 1.29 mmol, 81 %).

^{1}H NMR ($CDCl_3$): δ 7.35–7.22 (m, 5H, Ar), 6.67 (bs, 1H, N-*H*), 5.29 (bs, 1H, N-*H*), 4.43 (d, 2H, *J* = 5.8 Hz, Ph-C*H*$_2$-N), 3.81 (d, 2H, *J* = 5.7 Hz, N-C*H*$_2$-C=O), 1.41 (s, 9H, C(C*H*$_3$)$_3$).[170]

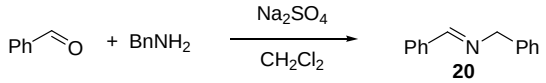
^{13}C NMR ($CDCl_3$): δ 169.5, 156.2 (2 × *C*=O), 138.0, 128.8, 127.8, 127.7 (Ar), 77.4 (*C*(CH$_3$)$_3$), 44.6, 43.5 (2 × -CH$_2$-), 28.4 (C(*C*H$_3$)$_3$).

The amide (296 mg, 1.12 mmol) from the previous reaction was weighted into a flask which was then cooled in an ice bath. TFA (4 mL) was then added slowly and the resulting solution was heated to 30 °C for 2 hours. Excess TFA was removed *in vacuo* and Et_2O was added to cause precipitation of the product. The product was washed thoroughly with Et_2O and dried. Yield: 255 mg, 0.92 mmol, 81 %. The amine was liberated by taking the compound up in CH_2Cl_2/aq. K_2CO_3, separating the phases, drying the organic phase and concentrating.

Free base:

^{1}H NMR ($CDCl_3$): δ 7.60 (bs, 1H, O=C-N-*H*), 7.37–7.23 (m, 5H, Ar), 4.47 (d, 2H, *J* = 6.0 Hz, Ph-C*H*$_2$-N), 3.40 (s, 2H, N-C*H*$_2$-C=O), 1.55 (bs, 2H, -N*H*$_2$).

^{13}C NMR (DMSO-*d6*): δ 163.1(*C*=O), 130.1, 120.0, 119.1, 118.7 (Ar), 34.5, 34.4 (2 × -*C*H_2-).



20

(*E*)-*N*-benzylidene(phenyl)methanamine (20)

Benzaldehyde (2.63 g, 24.7 mmol, 2.5 mL) was added to CH_2Cl_2 (30 mL) followed by $BnNH_2$ (2.70 g, 25.2 mmol, 2.75 mL) and Na_2SO_4 (10 g). The suspension was stirred at r.t. for 2 hours and then filtered and concentrated to give the imine as a sticky solid (4.82 g, 24.7 mmol, quant. yield).

Procedure taken from ref. 171.

^{1}H NMR ($CDCl_3$): δ 8.44 (t, 1H, *J* = 1.2 Hz, *H*-C=N), 7.89–7.82 (m, 2H, Ar), 7.50–7.30 (m, 8H, Ar), 4.89 (d, 2H, *J* = 1.2 Hz, Ph-C*H*$_2$-N).

^{13}C NMR ($CDCl_3$): δ 162.0 (*C*=N) 139.3, 136.2, 130.8, 128.6, 128.5, 128.3, 128.0, 127.0 (Ar), 65.0 Ph-*C*H_2-N).

MS: *m/z* 195 [M].

6.1.2.3 Synthesis of ligands

$PCyp_3$ → $PCyp_3$·HBF_4

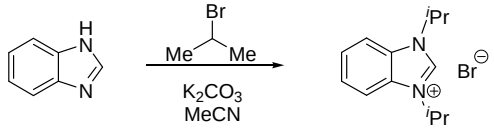
Tricyclopentylphosphine tetrafluoroborate

$PCyp_3$ (200 mg, 0.20 mL, 0.84 mmol) was added to CH_2Cl_2 (5 mL; dry, degassed) under Ar. HBF_4 (48 % in H_2O, 2.4 mmol, 311 μL) was added drop-wise and the mixture was stirred vigorously for 10 min. before water (2 mL) was added. Stirring continued for 5 min. and the organic phase was removed by pipette. CH_2Cl_2 (5 mL) was added to the aqueous phase and the mixture was stirred for 5 min. and the organic phase was removed (repeat once more). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was taken up in a minimum of acetone and heptane was added to cause precipitation. Filtration gave the desired product (205 mg, 0.63 mmol, 75 %).

^{1}H NMR ($CDCl_3$): δ 6.10 (qd, 1H, *J* = 5.7 Hz, *J* = 472.5 Hz, P-*H*), 2.74–2.55 (m, 3H, C*H*-P), 2.25–2.13 (m, 6H, 3 × -C*H*$_2$-), 1.90–1.65 (m, 18H, 9 × -C*H*$_2$-).

^{13}C NMR ($CDCl_3$): δ 29.2 (d, *J* = 1.2 Hz, *C*H_2-*C*H_2-CH_2-CH-P), 28.4 (d, *J* = 45.7 Hz, *C*H-P), 26.0 (d, *J* = 11.1 Hz, 2 × *C*H_2-CH-P).

Procedure and NMR data is available in reference 83.



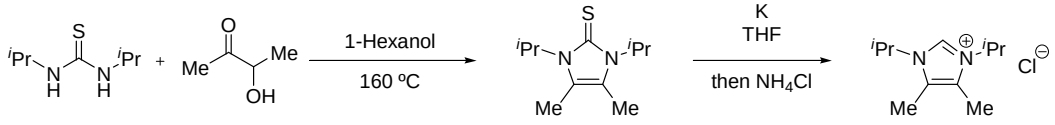
1,3-Diisopropylbenzimidazolium bromide

A flask was charged with benzimidazole (600 mg, 5.08 mmol), K_2CO_3 (790 mg, 5.72 mmol), and MeCN (3 mL). The suspension was stirred at r.t. for one hour before 2-bromopropane (3.69 g, 2.8 mL, 30 mmol) was added and the mixture was heated to reflux temperature. After 18 hours another 1.4 mL of 2-bromopropane was added and stirring continued for two days. The mixture was cooled to r.t. and the volatiles were removed under reduced pressure. To the residue was added CH_2Cl_2 (20 mL) and the mixture was filtered through Celite®. The filter aid was washed with more CH_2Cl_2 (~ 30 mL). The solvent was removed and to the resulting brown syrup was added EtOAc until the product precipitated. The solid was filtered off and washed with EtOAc. Yield: 766 mg, 2.7 mmol, 53 %.

^{1}H NMR ($CDCl_3$): δ 11.13 (s, 1H, N=C*H*-N), 7.80 (dd, 2H, *J* = 3.2 Hz, *J* = 6.2 Hz, Ar), 7.58 (dd, 2H, *J* = 3.1 Hz, *J* = 6.4 Hz, Ar), 5.15 (septet, 2H, *J* = 6.8 Hz, C*H*$(Me)_2$), 1.77 (d, 12H, *J* = 6.8 Hz, -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 140.0 (N=*C*H-N), 130.7, 127.0, 113.9 (Ar), 52.1, (*C*H$(Me)_2$), 22.2 (-*C*H_3).

Procedure taken from ref. 172.



1,3-Diisopropyl-4,5-dimethylimidazolium chloride

1,3-Diisopropyl-2-thiourea (1.6 g, 10.0 mmol) and 3-hydroxy-2-butanone (0.88 g, 10 mmol) were added to a flask containing 1-hexanol (25 mL). The mixture was heated to 160 °C for 16 hours. After cooling to r.t. the volatiles were removed *in vacuo*. The solid

residue was washed with water and a minimum of Et_2O before the intermediate was recrystallized from H_2O/EtOH (1:1). Yield: 180 mg, 0.85 mmol, 8 %.

^{1}H NMR ($CDCl_3$): δ 5.67 (bs, 2H, C*H*$(Me)_2$), 2.18 (s, 6H, =C-C*H*$_3$), 1.43 (d, 12H, *J* = 7.1 Hz, CH(C*H*$_3)_2$). For NMR data, see reference 68a.

The thione (53 mg, 0.25 mmol) was weighted into a flame dried Schlenk-flask and vacuum was applied. The flask was refilled with Ar (repeat twice). THF (5 mL) was added and the solution was cooled to 0 °C before potassium (25 mg, 39 mmol) was added. The mixture was then heated to reflux temperature for 18 hours. After cooling to r.t. NH_4Cl (~50 mg) was added and stirring continued for 10 min. before 2-propanol (2 mL) was added. The reaction mixture was then filtered through Celite® and removal of the volatiles gave the desired imidazolium salt (50 mg, 0.23 mmol, 92 %).

^{1}H NMR ($CDCl_3$): δ 10.57 (s, 1H, N=C*H*-N), 4.48 (septet, 2H, *J* = 6.4 Hz, C*H*$(Me)_2$), 2.24 (s, 6H, C=C-C*H*$_3$), 1.64 (d, 12H, *J* = 6.6 Hz, CH(C*H*$_3)_2$).

^{13}C NMR ($CDCl_3$): δ 134.0 (N=*C*H-N), 125.5 (*C*=*C*), 51.2 (*C*H$(Me)_2$), 22.9 (=C-*C*H$_3$), 8.9 (CH(*C*H$_3)_3$).

Part of the procedure was taken from ref. 68a.

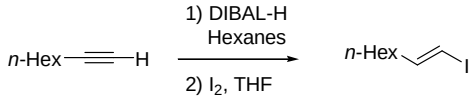
6.2 Work done at Princeton University

6.2.1 General information

Commercial reagents were used as received unless otherwise indicated. Organic solutions were concentrated on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using force-flow chromatography on Silicycle 230–400 mesh silica gel or Iatrobeads 6RS-8060. TLC was performed on Silicycle 0.25 mm silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by staining with anisaldehyde, iodine on silica, CAM, or $KMnO_4$. Supercritical fluid chromatography was performed on a Mettler Toledo instrument (equipped with a variable wavelength detector and an ASH column and 5 % hexanes as the modifier) and was used to determine *ee* and d.r. GC-yields were measured on a Agilent Technologies 6850 GC-system with a Dex-CB column. IR-spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). NMR spectra were recorded on a 400 MHz Bruker

instrument, and the spectra are referenced to solvent residual signals according to literature values.[133] Reaction kinetics were measured using a Mettler Toledo RactIR iC10 apparatus. Temperatures below room temperature (except 0 and -78 °C) were maintained by a NESLAB CB-80 cryo-cool. Automated synthesis experiments were carried out on a ChemSpeed Technologies Accelerator Synthesizer. All solvents except acetone were purified according to the method of Grubbs.[173] Acetone was dried over Drierite® under argon and distilled immediately before use.

6.2.2 Synthesis of substrates



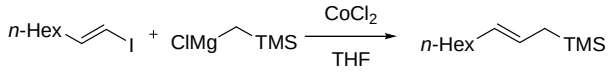
(*E*)-1-Iodooct-1-ene (59)

1-Octyne (2.06 g, 18.7 mmol) was added to a two-necked flask under argon. DIBAL-H (1 M in hexanes, 18.7 mL) was then added slowly, and the solution was heated to 50 °C for 5 hours. The solution was cooled to -78 °C and THF (20 mL) was added followed by drop-wise addition of a solution of I_2 (4.82 g, 19 mmol) in THF (5 mL). After complete addition the reaction mixture was stirred at -78 °C for 2 hours and then slowly heated to room temperature. The reaction was then cooled to 0 °C and quenched by careful addition of conc. H_2SO_4, and the mixture was poured into 20 % H_2SO_4/ice and extracted with pentane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (eluent: pentane) to give the product as a clear oil (4.03 g, 16.9 mmol, 91 %).

^{1}H NMR ($CDCl_3$): δ 6.51 (dt, 1H, *J* = 7.2 Hz, *J* = 14.4 Hz, *H*C=CI), 5.96 (ddd, 1H, *J* = 1.4 Hz, *J* = 2.8 Hz, *J* = 14.3 Hz, C=C*H*I), 2.05 (m, 2H, CH_2-HC=C), 1.43–1.19 (m, 8H, 4 × -CH_2-), 0.88 (t, 3H, *J* = 7.0 Hz, -CH_3).

^{13}C NMR ($CDCl_3$): δ 146.9 (H*C*=CI), 74.4 (I*C*=C), 36.2, 31.7, 28.7, 28.4, 22.7 (5 × -*C*H_2-), 14.2 (-*C*H_3).

For the procedure and NMR data, see reference 107.



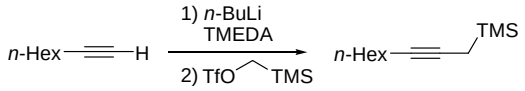
Trimethyl((*E*)-non-2-enyl)silane (57)

In the glove-box $CoCl_2$ (110 mg, 0.85 mmol) was weighted into a flask which was then sealed with a septum, and transferred to the fume hood. THF (15 mL) was added and the suspension was cooled to -78 °C before vinyl iodide (**59**; 2.0 g, 8.5 mmol) was added followed by slow addition of the Grignard reagent (1 M in Et_2O, 25.5 mL, 25.5 mmol). The brown solution stirred for 5 hours while slowly reaching room temperature. After stirring for 30 min at r.t. the solution was cooled to 0 °C and sat. aq. NH_4Cl (10 mL) was added. The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The allylsilane was obtained as a clear oil after column chromatography (eluent: pentane). Yield: 1.55 g, 7.8 mmol, 92 %. After the *Z*-isomer had been synthesized GC-analysis showed that the *E*/*Z* ratio for **57** was >99:1.

^{1}H NMR ($CDCl_3$): δ 5.36 (dt, 1H, *J* = 7.9 Hz, *J* = 15.7 Hz, *H*C=C), 5.27–5.20 (m, 1H, *H*C=C), 1.97 (q, 2H, *J* = 6.7 Hz, -C*H*$_2$-C=C), 1.40 (d, 2H, *J* = 7.9 Hz, =C-C*H*$_2$-TMS), 1.36–1.21 (m, 8H, 4 × -C*H*$_2$-), 0.88 (t, 3H, *J* = 7.0 Hz, -C*H*$_3$), -0.02 (s, 9H, TMS).

^{13}C NMR ($CDCl_3$): δ 129.2, 126.0 (*C*=*C*), 33.0, 31.9, 30.2, 29.0, 22.9, 22.7 (6 × -*C*H$_2$-), 14.3 (-*C*H$_3$), -1.9 (TMS).

For the procedure, see reference 108. For NMR data, see reference 174.



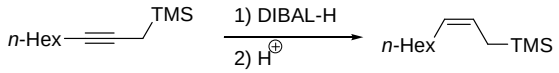
Trimethyl(non-2-ynyl)silane

1-Octyne (4.48 g, 40.7 mmol) was added to Et_2O (100 mL) under argon at -78 °C. *n*-BuLi (1.6 M in hexanes, 28 mL, 44.7 mmol) was then added slowly followed by TMEDA (1 mL). After 5 minutes the triflate (10.6 g, 8.9 mL, 44.7 mmol) was added drop-wise. The resulting mixture was stirred for 30 min. at -78 °C before it was allowed to slowly reach room temperature. After an additional 30 min. the reaction was quenched by careful addition of water, and the mixture was then poured into water (50 mL). The phases were separated and the aqueous phase was extracted twice with Et_2O (20 mL).

The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (elunet: pentane) and the desired product was obtained as a clear oil (8.1 g, quant. yield).

^{1}H NMR ($CDCl_3$): δ 2.16–2.07 (m, 2H, -C*H*$_2$-), 1.51–1.12 (m, 10H, 5 × -C*H*$_2$-), 0.87 (d, 3H, *J* = 7.1 Hz, CH_2-C*H*$_3$), 0.08 (s, 9H, TMS).

^{13}C NMR ($CDCl_3$): δ 79.1, 77.4 (*C*≡*C*), 31.6, 29.6, 28.7, 22.8, 19.0 (5 × -CH_2-), 14.2 (CH_2-*C*H_3), 7.0 (TMS-*C*H_2-), -2.0 (TMS).[175]

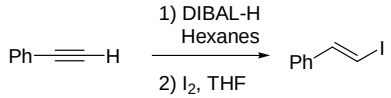


Trimethyl((*Z*)-non-2-enyl)silane (58)

The alkyne from the previous reaction (158 mg, 0.80 mmol) was weighed into a flask under argon and DIBAL-H (1 M in hexanes, 1.6 mL, 1.6 mmol) was added slowly. After complete addition the reaction mixture was heated to 70 °C for 4 hours, and then cooled to room temperature. 10 % HCl was then added carefully followed by water (10 mL) and pentane (15 mL). The phases were then separated and the aqueous phase was extracted with pentane (20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (eluent: pentane) and the product was obtained as a clear oil (121 mg, 0.61 mmol, 76 %). *Z*/*E* >99:1 (by GC).

^{1}H NMR ($CDCl_3$): δ 5.38 (dtt, 1H, *J* = 1.6 Hz, *J* = 8.5 Hz, *J* = 10.1 Hz, *H*C=C), 5.30–5.23 (m, 1H, *H*C=C), 1.98 (q, 2H, *J* = 6.5 Hz, C*H*$_2$-C=), 1.47 (d, 2H, *J* = 8.6 Hz, =C-C*H*$_2$-TMS), 1.38–1.21 (m, 8H, 4 × -C*H*$_2$-), 0.89 (t, 3H, *J* = 7.1 Hz, -C*H*$_3$), 0.01 (s, 9H, (TMS).[176]

^{13}C NMR ($CDCl_3$): δ 128.0, 125.4 (*C*=*C*), 32.0, 30.0, 29.3, 27.2, 22.8, 18.5 (6 × -*C*H_2-), 14.3 (-C*H*$_3$), -1.6 (TMS).[174]

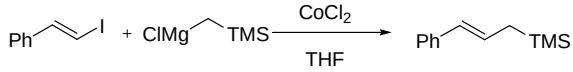


(*E*)-2-Phenyl-1-iodoethene

Same method as for **59**. Starting from 0.93 g (1 mL, 9.1 mmol) phenylacetylene 1.21 g (5.3 mmol, 58 %) of the vinyliodide was obtained.

^{1}H NMR ($CDCl_3$): δ 7.54 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz, Ar), 7.50–7.43 (m, 2H, Ar), 7.41–7.27 (m, 2H, Ar), 6.87 (s, 1H, *H*C=C), 6.84 (s, 1H, *H*C=C).

^{13}C NMR ($CDCl_3$): δ 145.0 (Ph-*C*H=C), 137.7, 128.8, 128.5, 126.1 (Ar), 76.9 (C=*C*HI).[177]

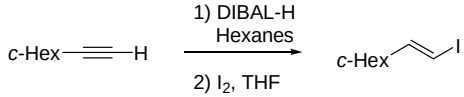


(*E*)-Cinnamyltrimethylsilane (62)

Same method as for **57**. Starting from 1.2 g vinyliodide (5.2 mmol) 626 mg of the allylsilane was obtained (3.3 mmol, 63 %).

^{1}H NMR ($CDCl_3$): δ 7.30–7.18 (m, 4H, Ar), 7.10 (tt, 1H, *J* = 1.5 Hz, *J* = 7.1 Hz, Ar), 6.24–6.15 (m, 2H, *H*-C=C-*H*), 1.65–1.58 (m, 2H, -CH_2-), 0.0 (2 × s, 9H, 3 × -CH_3).

^{13}C NMR ($CDCl_3$): δ 138.6, 128.6, 128.3, 128.0, 126.3, 125.6 (Ar, *C*=*C*), 24.1 (-*C*H_2-), -1.7 (-*C*H_3).[178]



((*E*)-2-Iodovinyl)cyclohexane

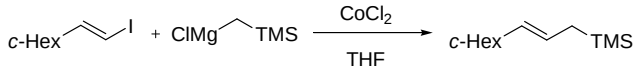
Same method as for **59**. The crude product was used directly for the next reaction

Crude NMR:

^{1}H NMR ($CDCl_3$): δ 6.48 (dd, 1H, *J* = 7.2 Hz, *J* = 14.5 Hz, *H*C=C), 5.95 (dd, 1H, *J* = 1.2 Hz, *J* = 14.5 Hz, *H*C=C), 2.08–1.94 (m, 1H, =C-C*H*<), 1.81–1.67 (m, 4H, -CH_2-), 1.30–1.03 (m, 6H, -CH_2-).

^{13}C NMR ($CDCl_3$): δ 152.3 (*H*C=C), 73.4 (C=*C*IH), 44.7 (=C-*C*H<), 32.1, 26.0, 25.8 (3 × -*C*H_2-).

For selected NMR data, see reference 179.

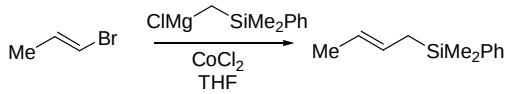


((*E*)-3-Cyclohexylallyl)trimethylsilane (63)

Same method as for **57**. Starting from 0.414 mg (0.5 mL, 3.8 mmol) cyclohexylacetylene 366 mg (1.86 mmol, 83 % over two steps) of the desired product was obtained as a clear oil.

^{1}H NMR ($CDCl_3$): δ 5.34 (dt, 1H, *J* = 7.9 Hz, *J* = 15.9 Hz, =C*H*-CH_2-), 5.20 (dd, 1H, *J* = 6.9 Hz, *J* = 15.3 Hz, =C*H*-CH<), 1.95–1.84 (m, 1H, =CH-C*H*<), 1.76–1.59 (m, 4H, -CH_2-), 1.39 (d, 2H, *J* = 8.2 Hz, TMS-CH_2-HC=), 1.34–0.98 (m, 6H, -CH_2-), -0.02 (s, 9H, TMS).[180]

^{13}C NMR ($CDCl_3$): δ 135.3, 123.4 (*C*=*C*), 41.2 (=C-*C*H<), 33.8, 26.4, 26.3, 22.7 (-CH_2-), -1.9, -1.9 (TMS).



((*E*)-But-2-enyl)dimethyl(phenyl)silane (65)

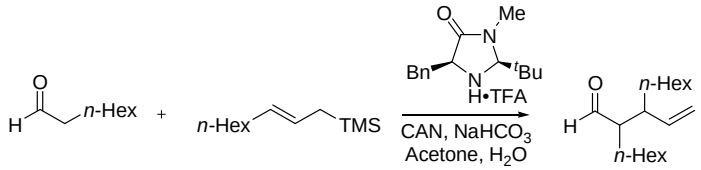
Same method as for **57** except that the Grignard reagent was prepared from magnesium and the corresponding chloromethylsilane in THF. From 141 mg (0.1 mmol) of the vinyl bromide was obtained 200 mg (quant. yield) of the allylsilane.

^{1}H NMR ($CDCl_3$): δ 7.54 (dd, 2H, *J* = 3.0 Hz, *J* = 6.5 Hz, Ar), 7.41–7.34 (m, 3H, Ar), 5.46–5.37 (m, 1H, *H*C=C), 5.35–5.26 (m, 1H, *H*C=C), 1.69–1.63 (m, 5H, -CH_2-, -CH_3), 0.30, 0.28 (2 × s, 6H, Si-(CH_3)$_2$).

^{13}C NMR ($CDCl_3$): δ 139.2, 133.8, 129.0, 127.8, 126.5, 124.1 (Ar, *C*=*C*), 21.7, 18.3 (-*C*H_2-, -*C*H_3), -3.2 (Si-(*C*H_3)$_2$).[181]

HRMS: 190.1178 (calc. for $C_{12}H_{18}Si$: 190.1179).

6.2.3 Allylation under SOMO conditions



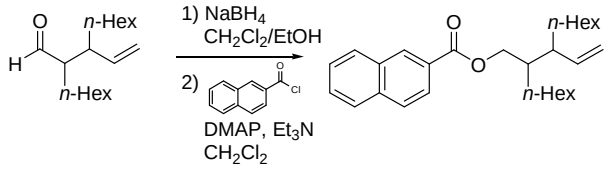
2-Hexyl-3-vinylnonanal (68)

Into a vial were weighted the catalyst (18 mg, 0.05 mmol), $NaHCO_3$ (32 mg, 0.38 mmol), and CAN (345 mg, 0.63 mmol) and the vial was capped and vacuum was applied. The vial was back-filled with argon and cooled to -78 °C before acetone (1 mL, freshly distilled) was added. The solvent was degassed by applying vacuum and stirring for 5 min. and back-filling with argon (repeated three times). Octanal (freshly distilled, 64 mg, 0.5 mmol), allylsilane (50 mg, 0.25 mmol), and water (9 mg, 0.5 mmol) were added, and the mixture was degassed once more. The mixture was then heated to -10 °C and stirred for 24 hours. The vial was then cooled to -78 °C and ether was added. The mixture was filtered through silica and the silica-pad was washed with ether. The volatiles were removed under reduced pressure and the residue was subjected to column chromatography (eluent: pentane, then pentane/ether 19:1), and the desired product was obtained as a clear oil (55 mg, 0.22 mmol, 50 %). The product was obtained as a 1:4 mixture of diastereomers.

Major isomer:

^{1}H NMR (Acetone-d_6): δ 9.58 (d, 1H, J = 3.7 Hz, -C*H*O), 5.60 (dt, 1H, J = 9.8 Hz, J = 17.1 Hz, -*H*C=CH_2), 5.12–4.99 (m, 2H, -HC=CH_2), 2.35–2.25 (m, 1H, -C*H*<), 2.22 (m, 1H, -C*H*<), 1.70–1.15 (m, 20H, -CH_2-), 0.88 (t, 3H, J = 6.9 Hz, -CH_3), 0.87 (t, 3H, J = 6.7 Hz, -CH_3).

^{13}C NMR (Acetone-d_6): δ 206.2 (*C*=O), 141.7 (-H*C*=C), 117.8 (C=*C*H_2), 57.3 (O=C-*C*H<), 46.7 (=C-*C*H<), 33.5, 33.4, 29.1, 28.9, 28.3, 28.3, 27.9, 24.3, 24.2 (10 × -*C*H_2-), 15.4, 15.2 (2 × -*C*H_3).



2-Hexyl-3-vinylnonyl 2-naphthoate

The aldehyde **68** was dissolved in CH_2Cl_2/EtOH (4:1; 5 mL) and $NaBH_4$ (~5 equiv.) was added. After stirring for 30 min. sat. aq. NH_4Cl (5 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. After column chromatography (eluent: pentane, then pentane/ether 19:1) the intermediate alcohol was obtained.

^{1}H NMR ($CDCl_3$): δ 5.68–5.58 (m, 1H, -*H*C=CH_2), 5.05–4.97 (m, 2H, -HC=C*H*$_2$), 3.62 (dd, 1H, *J* = 5.0 Hz, *J* = 11.1 Hz, HO-C*H*H'), 3.55 (dd, 1H, *J* = 5.3 Hz, *J* = 11.1 Hz, HO-CH*H*'-), 2.10–2.00 (m, 1H, -C*H*<), 1.46–1.12 (m, 21H, 10 × -CH_2-, -C*H*<), 0.90–0.85 (m, 6H, 2 × -C*H*$_3$).

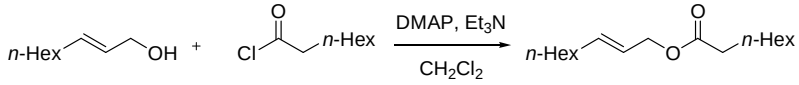
^{13}C NMR ($CDCl_3$): δ 141.6, 115.4 (*C*=*C*), 63.7 (HO-*C*H_2-), 45.6, 44.9 (2 × -*C*(Hex)H-), 32.0, 31.9, 29.7, 29.4, 28.9, 27.6, 27.3, 22.7 (-*C*H_2-), 14.2, 14.1 (2 × -*C*H_3).

The alcohol was then taken up in CH_2Cl_2 (5 mL) and 2-naphthoyl chloride (~30 mg), DMAP (one crystal), and Et_3N (1 mL) were added and the resulting solution was stirred at room temperature overnight. Water (5 mL) was added, the phases were separated, and the aqueous phase was extracted once with CH_2Cl_2 (5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The desired product was obtained as a clear oil after column chromatography (eluent: pentane/Et_2O 19:1).

^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H, Ar), 8.06 (ddd, 1H, *J* = 1.7 Hz, *J* = 3.3 Hz, *J* = 8.6 Hz, Ar), 7.96 (d, 1H, *J* = 8.1 Hz, Ar), 7.90 (s, 1H, Ar), 7.88 (s, 1H, Ar), 7.60 (m, 1H, Ar), 7.55 (ddd, 1H, *J* = 1.1 Hz, *J* = 7.0 Hz, *J* = 7.9 Hz, Ar), 5.65 (m, 1H, -*H*C=CH_2), 5.10–5.05 (m, 1H, -HC=C*H*H'), 5.02 (ddd, 1H, *J* = 1.5 Hz, *J* = 4.8 Hz, *J* = 17.1 Hz, -HC=CH*H*'), 4.38 (m, 1H, O-C*H*H'-CH<), 4.29–4.24 (m, 1H, O-CH*H*'-CH<), 2.23–2.15 (m, 1H, -C*H*<), 1.93–1.79 (m, 1H, -C*H*<), 1.59–1.17 (m, 20H, -C*H*$_2$-), 0.87 (t, 3H, *J* = 6.4 Hz, -C*H*$_3$), 0.86 (t, 3H, *J* = 6.9 Hz, -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 167.0 (*C*=O), 140.4, 135.6, 132.6, 131.1, 129.5, 128.3, 128.3, 127.9, 127.9,126.7, 125.4 (Ar, -H*C*=CH_2), 116.1 (Ar, -HC=*C*H_2), 66.2 (C(=O)-O-*C*H_2-), 45.8, 41.6 (2 × -*C*(Hex)H-), 32.0, 29.7, 29.6, 27.3, 22.8, 22.8 (-*C*H_2-), 14.3 (-*C*H_3).

6.2.4 Determination of stereochemistry



(*E*)-Non-2-enyl octanoate (70)

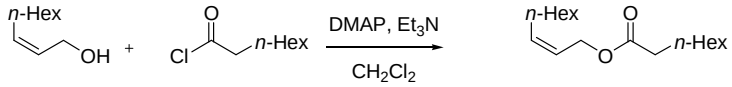
The alcohol (1.68 g, 11.8 mmol) and acid chloride (2.29 g, 14.1 mmol) were added to dry CH_2Cl_2 (40 mL) under argon followed by Et_3N (2.32 g, 23 mmol, 3.2 mL) and DMAP (30 mg). The resulting solution was then stirred at room temperature while being monitored by TLC (pentane/Et_2O 5:1). After one hour complete consumption of the alcohol was observed, and the reaction was quenched by addition of water (10 mL). The mixture was transferred to a separatory funnel and sat. aq. NH_4Cl (20 mL) was added. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2 (20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (eluent: pentane/Et_2O 5:1) to give the ester as a colorless oil. Yield: 3.16 g, quantitative yield.

^{1}H NMR ($CDCl_3$): δ 5.75 (dt, 1H, *J* = 6.7 Hz, *J* = 15.0 Hz, *H*C=C), 5.55 (dt, 1H *J* = 6.5 Hz, *J* = 14.9 Hz, *H*C=C), 4.50 (d, 2H, *J* = 6.5, O-C*H*$_2$-HC=), 2.29 (t, 2H, *J* = 7.6 Hz, O=C-C*H*$_2$-), 2.05 (d, 1H *J* = 6.7 Hz, -C*H*H'-HC=), 2.02 (d, 1H, *J* = 7.0 Hz, -CH*H*'-HC=), 1.67–1.55 (m, 2H, -C*H*$_2$-), 1.42–1.18 (m, 16H, 8 × -C*H*$_2$-), 0.93–0.82 (m, 6H, 2 × -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 173.8 (*C*=O), 136.7, 123.9 (*C*=*C*), 65.2 (=C-*C*H_2-O-), 34.5, 32.4, 31.8, 31.8, 29.2, 29.1, 29.0, 25.1, 22.7 (11 × -*C*H_2-), 14.2, 14.2 (2 × -*C*H_3).

IR (neat): 2955.76, 2925.32, 2856.08, 1736.85, 1458.55, 1379.35, 1162.05, 967.53.

HRMS: 268.2401 (calc. for $C_{17}H_{32}O_2$: 268.2402).



(*Z*)-non-2-enyl octanoate (71)

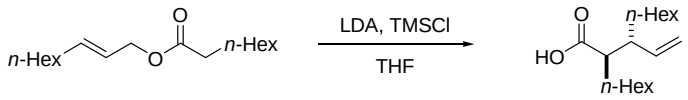
Same procedure as for **70**

^{1}H NMR ($CDCl_3$): δ 5.67–5.61 (m, 1H, *H*C=C), 5.55–5.49 (m, 1H, *H*C=C), 4.61 (d, 2H, *J* = 6.9 Hz, O-C*H*$_2$-HC=), 2.30 (t, 2H, *J* = 7.6 Hz, O=C-C*H*$_2$-), 2.09 (q, 2H, *J* = 7.0 Hz, -C*H*$_2$-HC=), 1.65–1.58 (m, 2H, -C*H*$_2$-), 1.40–1.20 (m, 16H, 8 × -C*H*$_2$-), 0.87 (2 × t, 6H, *J* = 6.9 Hz, *J* = 7.0 Hz, 2 × -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 174.0 (*C*=O), 135.6, 123.4 (*C*=*C*), 60.3 (=C-C*H*$_2$-O-), 34.5, 31.8, 31.8, 29.5, 29.2, 29.1, 29.0, 27.7, 25.1, 22.8, 22.7 (11 × -*C*H$_2$-), 14.2, 14.2 (2 × -*C*H$_3$).

IR (neat): 2956.01, 2925.39, 2856.23, 1736.52, 1458.51, 1377.56, 1161.84, 969.43

HRMS: 268.2403 (calc. for $C_{17}H_{32}O_2$: 268.2402).



(2*R, 3*R**)-2-hexyl-3-vinylnonanoic acid (72)**

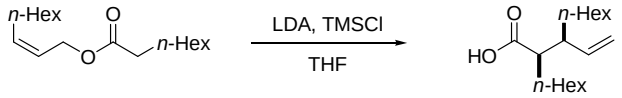
To diisopropylamine (45 mg, 0.45 mmol, 63 µL) in dry THF (1 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 0.26 mL, 0.41 mmol) and the resulting solution was stirred for 5 min. and then cooled to -78 °C. The ester **70** (100 mg, 0.37 mmol, 125 µL) was added slowly. After 5 min. was TMSCl (44.5 mg, 0.41 mmol, 52 µL) added and the reaction mixture was heated first to room temperature and then to 60 °C for 5 hours. TLC analysis (pentane/Et_2O 6:1 + 2 drops HCOOH) showed incomplete conversion but the reaction was stopped (cooled to r.t. followed by addition of MeOH) to avoid isomerization. Water (5 mL) was added to the mixture and the product was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Column chromatography (eluent: pentane/Et_2O 6:1 + 2 % HCOOH) gave the product as a white solid (48 mg, 0.18 mmol, 48 %).

^{1}H NMR ($CDCl_3$): δ 5.44 (dt, 1H, *J* = 9.6 Hz, *J* = 16.9 Hz, -*H*C=CH$_2$), 5.08 (dd, 1H, *J* = 1.5 Hz, *J* = 10.2 Hz, =C*H*H'), 5.02 (dd, 1H, *J* = 1.5 Hz, *J* = 17.0 Hz, =CH*H*'), 2.28–2.18 (m, 2H, 2 × -C*H*<), 1.57–1.44 (m, 2H, -C*H*$_2$-), 1.44–1.11 (m, 18H, 9 × -C*H*$_2$-), 0.86 (6H, t, *J* = 6.7 Hz, 2 × -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 182.1 (*C*=O), 139.7 (-H*C*=CH_2), 117.1 (-HC=*C*H_2), 50.5 (-*C*H<), 47.0 (-*C*H<), 32.8, 31.9, 31.8, 30.1, 29.4, 29.3, 27.7, 27.3, 22.8, 22.7 (10 × -*C*H_2-), 14.3, 14.2 (2 × -*C*H_3).

IR (neat): 2953.77, 2921.06, 2853.45, 1704.59, 1467.75, 1295.05, 1260.54, 1221.04, 999.23, 929.19.

HRMS: 268.2403 (calc. for $C_{17}H_{32}O_2$: 268.2402).



(2*R, 3*S**)-2-hexyl-3-vinylnonanoic acid (73)**

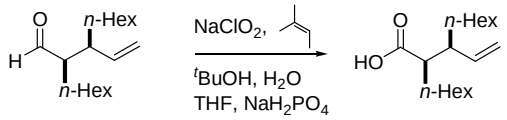
Same method as for **72**. The product was obtained as a clear oil. Yield: 40 mg, 0.15 mmol, 40 %.

^{1}H NMR ($CDCl_3$): δ 5.63 (dt, 1H, *J* = 10.1 Hz, *J* = 17.1 Hz, -*H*C=CH_2), 5.04 (dd, 1H, *J* = 1.8 Hz, *J* = 10.3 Hz, HC=C*H*H'), 5.00 (dd, 1H, *J* = 1.5 Hz, *J* = 17.2 Hz, HC=CH*H*'), 2.37–2.31 (m, 1H, -C*H*<), 2.22–2.13 (m, 1H, -C*H*<), 1.68–1.40 (m, 3H, -CH_2-), 1.38–1.14 (m, 17H, -CH_2-), 0.87 (t, 6H, *J* = 6.9 Hz, 2 × -CH_3)

^{13}C NMR ($CDCl_3$): δ 181.0 (*C*=O), 139.5 (-H*C*=CH_2), 116.5 (-HC=*C*H_2), 50.3, 46.7 (2 × -*C*H<), 32.1, 31.9, 31.8, 30.0, 29.4, 29.4, 27.8, 27.3, 22.8, 22.8 (10 × -*C*H_2-), 14.3, 14.2 (2 × -*C*H_3).

IR (neat): 2956.34, 2926.24, 2857.25, 1705.37, 1458.97, 1417.19, 1228.43, 994.01, 915.41.

HRMS: 268.2405 (calc. for $C_{17}H_{32}O_2$: 268.2402).



(2*R, 3*S**)-2-hexyl-3-vinylnonanoic acid (73) by oxidation of SOMO-product (68)**

The aldehyde (**68**; 15 mg, 0.06 mmol) was dissolved in ^{t}BuOH/THF (1:1, 1.0 mL) and NaH_2PO_4 (2 mg, 0.015 mmol) and 2-methyl-2-butene (6.3 mg, 9.5 µL, 0.09 mmol) were added followed by a solution of $NaClO_2$ (8.1 mg, 0.09 mmol) in water at 0 °C. The mixture was stirred at this temperature for one hour and then for one hour at room

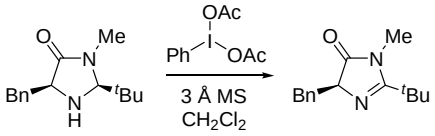
temperature before the reaction was quenched by addition of sodium sulfite and after 5 min. 1 M HCl (1 mL). EtOAc (5 mL) was added, the phases were separated and the aqueous phase was extracted twice with EtOAc (5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to dryness. The residue was purified by column chromatography (eluent: pentane/Et_2O 6:1 + 1 % HCOOH) to give the title compound (9 mg, 0.034 mmol, 56 %).

Major isomer:

^{1}H NMR ($CDCl_3$): δ 5.64 (1H, dt, *J* = 9.9 Hz, *J* = 17.1 Hz, -*H*C=CH_2), 5.10–4.96 (m, 2H, -HC=C*H*$_2$), 2.40–2.30 (m, 1H, -C*H*<), 2.28–2.11 (m, 1H, -C*H*<), 1.67–1.12 (m, 20H, -C*H*$_2$-), 0.91–0.81 (m, 6H, 2 × -C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ 181.1 (*C*=O), 139.5 (H*C*=CH_2), 116.5 (HC=*C*H_2), 50.3, 46.7 (2 × -*C*H<), 32.1, 31.9, 31.8, 30.0, 29.4, 29.4, 27.8, 27.3, 22.8, 22.7 (10 × -*C*H_2), 14.3, 14.2 (2 × -*C*H_3).

6.2.5 Catalyst development



(*S*)-2-*tert*-butyl-4-benzyl-1-methyl-1*H*-imidazol-5(4*H*)-one (77)

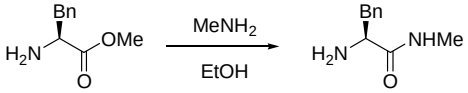
Iodobenzene diacetate (403 mg, 1.25 mmol) and freshly activated 3 Å MS (100 mg) were weighted into a vial (oven dried) and vacuum was applied. The vial was filled with argon and CH_2Cl_2 (5 mL) was added. The mixture was stirred for ten minutes before the amine (62 mg, 0.25 mmol) was added. The resulting mixture was stirred for 6 hours and the mixture was then filtered through Celite® and concentrated. The residue was subjected to column chromatography on Iatrobeads (eluent: pentane/Et_2O 1:1 then 1:2) to give the desired product as a clear oil (53 mg, 0.22 mmol, 88 %).

^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2H, *J* = 7.6 Hz, Ar), 7.29 (t, 2H, *J* = 7.5 Hz, Ar), 7.22 (t, 1H, *J* = 7.3 Hz, Ar), 4.74 (s, 1H, Bn-C*H*<), 3.96 (dd, 1H, *J* = 14.5 Hz, *J* = 1.6 Hz, Ph-C*H*H'-), 3.89 (dd, 1H, *J* = 14.5 Hz, *J* = 0.6 Hz, Ph-CH*H*'-), 3.07 (s, 3H, N-C*H*$_3$), 0.97 (s, 9H, -C(C*H*$_3$)$_3$).

^{13}C NMR ($CDCl_3$): δ 169.0, 165.3 (*C*=O, *C*=N), 135.6, 129.5, 128.7, 126.9 (Ar), 91.8 (Bn-*C*H<), 36.7 (-*C*Me$_3$), 35.1 (Ph-*C*H$_2$-) 31.2 (N-*C*H$_3$), 26.3 (-C(*C*H$_3$)$_3$).

IR (neat): 2959.06, 2936.02, 2871.09, 1704.89, 1637.31, 1455.09, 1425.77, 1396.22, 1365.92, 749.59, 700.85.

For the procedure and characterization, see reference 122.

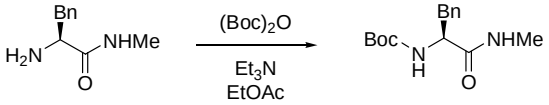


L-Phenylalanine methylamide (79)

To L-phenylalanine methyl ester (500 mg, 2.79 mmol) was added $MeNH_2$ (33 % in EtOH; 20 mL) and the solution was stirred at room temperature for 18 hours. Removal of the solvent and methyl amine under reduced pressure gave a solid residue that was suspended in a minimum of Et_2O. After stirring for one hour the solid was filtered off and dried under vacuum. Yield: 453 mg, 2.54 mmol, 91 %.

^{1}H NMR ($CDCl_3$): δ 7.38–7.21 (m, 6H, Ar, C(=O)N*H*), 3.62 (dd, 1H, *J* = 3.3 Hz, *J* = 9.4 Hz, >C*H*-Bn), 3.31 (dd, 1H, *J* = 3.4 Hz, *J* = 13.7 Hz, Ph-C*H*H'-), 2.84 (d, 3H, *J* = 5.0 Hz, N-C*H*$_3$), 2.68 (dd, 1H, *J* = 9.7 Hz, *J* = 13.6 Hz, Ph-CH*H*'-), 1.35 (bs, 2H, -N*H*$_2$).

^{13}C NMR ($CDCl_3$): δ 174.9 (*C*=O), 138.1, 129.4, 128.8, 126.9 (Ar), 56.6 (-*C*H<), 41.1 (Ph-*C*H$_2$-), 26.0 (N-*C*H$_3$).[182]

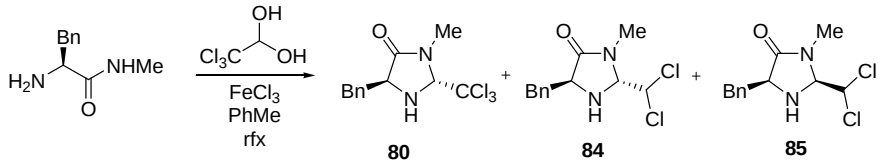


***N*-Boc-L-phenylalanine methylamide (82)**

The amine (**79**; 200 mg, 1.1 mmol) was added to EtOAc (5 mL) followed by Et_3N (0.16 mL, 1.1 mmol) and $(Boc)_2O$ (240 mg, 1.1 mmol). The resulting mixture was stirred for 30 minutes and TLC (eluent: MeOH/Et_3N/EtOAc 1:1:18) showed full conversion of the starting material. The mixture was transferred to a separatory funnel and washed with water (10 mL), sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated to give the title product as a white solid (317 mg, 1.1 mmol, quant. yield).

^{1}H NMR ($CDCl_3$): δ 7.29–7.04 (m, 5H, Ar), 5.85 (bs, 1H), 5.05 (bs, 1H), 4.24 (bs, 1H, 2 × N-*H*, -C*H*<), 2.98 (bs, 2H, Ph-CH_2-), 2.65 (d, 3H, *J* = 4.0 Hz, N-CH_3), 1.32 (s, 9H, C(CH_3)$_3$).

^{13}C NMR ($CDCl_3$): δ 171.9 (*C*(=O)N), 155.6 (O-*C*(=O)N), 136.9, 129.4, 128.7, 127.0 (Ar), 80.2 (-*C*(CH_3)$_3$), 56.1 (-*C*H<, 38.9 (Ph-*C*H_2-, 28.4 (-C(*C*H_3)$_3$), 26.3 (N-*C*H_3).[183]



(2*R*,5*S*)-5-benzyl-2-(trichloromethyl)-3-methylimidazolidin-4-one (80)

(2*R*,5*S*)-5-benzyl-2-(dichloromethyl)-3-methylimidazolidin-4-one (84)

(2*S*,5*S*)-5-benzyl-2-(dichloromethyl)-3-methylimidazolidin-4-one (85)

The amine **79** (200 mg, 1.1 mmol), chloral hydrate (186 mg, 1.13 mmol), and $FeCl_3$ (36 mg, 0.22 mmol) were weighted into a flask and vacuum was applied. The flask was filled with argon and PhMe (10 mL) was added. The reaction mixture was then heated to reflux for 18 hours. The reaction was monitored by TLC (eluent: EtOAc/pentane 7:3). No further conversion was observed and the mixture was cooled to room temperature before sat. aq. $NaHCO_3$ (5 mL) was added. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (eluent: EtOAc/pentane gradient 1:10 → 100 % EtOAc). **80**, **84**, and **85** were obtained as pale yellow solids in 5, 13, and 3 % yield respectively.

80:

^{1}H NMR ($CDCl_3$): δ 7.37–7.18 (m, 5H, Ar), 4.70 (s, 1H, >C*H*-CCl_3), 4.20–4.08 (m, 1H, Bn-C*H*<), 3.16 (dd, 1H, *J* = 4.0 Hz, *J* = 14.0 Hz, Ph-C*H*H'-), 3.10 (s, 3H, N-CH_3), 2.88 (dd, 1H, *J* = 7.5 Hz, *J* = 14.0 Hz, Ph-CH*H*'-), 1.64 (s, 1H, N-*H*).

^{13}C NMR ($CDCl_3$): δ 174.9 (*C*=O), 136.8, 129.5, 128.9, 127.1 (Ar), 103.5 (-*C*Cl_3), 85.6 (>*C*H-CCl_3), 58.8 (Bn-*C*H<), 39.0 (Ph-*C*H_2-), 31.2 (N-*C*H_3).

MS: 306.8 (calc. for $C_{12}H_{13}Cl_3N_2O$: 306.0).

84:

^{1}H NMR ($CDCl_3$): δ 7.38–7.17 (m, 5H, Ar), 5.79–5.72 (m, 1H, -C*H*Cl_2), 4.54 (bs, 1H, >C*H*-$CHCl_2$), 4.06 (bs, 1H, Bn-C*H*<), 3.18–3.10 (m, 1H, Ph-C*H*H'-), 2.95 (dd, 1H, *J* = 7.0 Hz, *J* = 14.1 Hz, Ph-CH*H*'), 2.89 (s, 3H, N-CH_3), 2.35 (bs, 1H, N-*H*).

^{13}C NMR ($CDCl_3$): δ 174.1 (*C*=O), 136.7, 129.6, 128.9, 127.1 (Ar), 78.6, 74.2 (-*C*H-*C*HCl_2), 59.5 (Bn-*C*H<), 38.7 (Ph-*C*H_2-), 28.1 (N-*C*H_3).

No nOe was observed between H2 and H5.

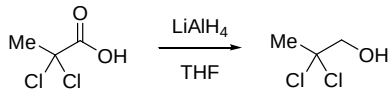
85:

^{1}H NMR ($CDCl_3$): δ 7.43–7.10 (m, 5H, Ar), 5.60 (s, 1H, -C*H*Cl_2), 4.88 (s, 1H, >C*H*-$CHCl_2$), 3.93 (dd, 1H, *J* = 3.0 Hz, *J* = 8.5 Hz, Bn-C*H*<), 3.17 (dd, 1H, *J* = 3.6 Hz, *J* = 13.9 Hz, Ph-C*H*H'), 3.02–2.94 (m, 1H, Ph-CH*H*'), 2.94 (s, 3H, N-CH_3).

^{13}C NMR ($CDCl_3$): δ 172.4 (*C*=O), 137.2, 129.7, 128.8, 127.1 (Ar), 77.7 (-*C*HCl_2), 72.6 (>*C*H-$CHCl_2$), 59.4 (Bn-*C*H<), 38.4 (Ph-*C*H_2-), 28.7 (N-*C*H_3).

A small nOe was observed between H-2 and H-5.

MS: 272.8 (calc. for $C_{12}H_{14}Cl_2N_2O$: 272.0).



2,2-dichloropropan-1-ol

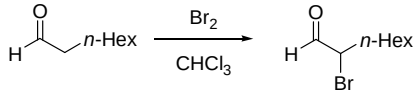
$LiAlH_4$ (2 M in THF, 7 mL, 14 mmol) was diluted with THF (7 mL), and cooled to 0 °C. 2,2-Dichloropropionic acid (2 g, 14.0 mmol) in THF (7 mL) was added at a rate sufficient to maintain a gentle reflux. The mixture was then heated to 70 °C for 15 min. and cooled to 0 °C before water (10 mL) was added. After the exothermic reaction had subsided 2 M H_2SO_4 (3 mL) was added to dissolve the precipitate. The mixture was then diluted with CH_2Cl_2 (15 mL) and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 (15 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (pentane/EtOAc 4:1) to give the primary alcohol as a clear oil (1.08 g, 8.4 mmol, 60 %)

^{1}H NMR ($CDCl_3$): δ 3.87 (d, 2H, *J* = 7.6 Hz, -CH_2OH), 2.68 (t, 1H, *J* = 7.5 Hz, O-*H*), 2.12 (s, 3H, -CH_3).

^{13}C NMR ($CDCl_3$): δ 89.8 (-*C*Cl_2-), 73.5 (-*C*H_2OH), 33.1 (-*C*H_3).

For the procedure, see ref. 184.

6.2.6 Substrate for photochemical reactions



2-Bromooctanal (88)

To a solution of octanal (1.28 g, 10 mmol) in $CHCl_3$ (2 mL) at 0 °C bromine (1.6 g, 10 mmol) was slowly added over 30 min. After an additional 30 min. the solution was allowed to reach room temperature and stirring continued for 30 min. Sat. aq. $NaHCO_3$ (5 mL) was added and the phases were separated. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (eluent: pentane/Et_2O 19:1) and the α-bromoaldehyde was obtained as a colorless oil (1.7 g, 8.2 mmol, 82 %).

^{1}H NMR ($CDCl_3$): δ 9.41 (d, 1H, *J* = 3.1 Hz, -C*H*O), 4.20 (ddd, 1H, *J* = 3.1 Hz, *J* = 6.2 Hz, *J* = 8.2 Hz, -C*H*Br-), 2.02 (m, 1H, CHBr-C*H*H'-), 1.89 (m, 1H, CHBr-CH*H*'-), 1.56–1.21 (m, 8H, 4 × -CH_2-), 0.87 (t, 3H, *J* = 7.0 Hz, -CH_3).[185]

^{13}C NMR ($CDCl_3$): δ 192.9 (*C*=O), 55.6 (-*C*HBr-), 31.7, 31.6, 28.7, 26.0, 22.6 (5 × -*C*H_2-), 14.1 (-*C*H_3).

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Appendix A

Nordstrøm, L. U.; Madsen, R. ’Iridium catalysed synthesis of piperazines from diols’, *Chem. Commun.* **2007**, 5034-5036.

Iridium catalysed synthesis of piperazines from diols†

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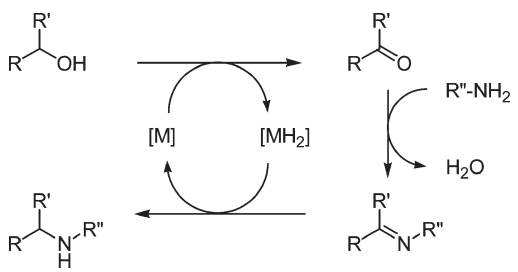
A green and atom-economical method has been developed for the synthesis of piperazines by cyclocondensation of diols and amines in aqueous media in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$.

The piperazine moiety is an important pharmacophore which is found in a large number of biologically active molecules. A recent survey of more than 1000 orally administered drugs showed that about 6% of these contained a piperazine fragment.[1] The synthesis of piperazines and substituted piperazines is usually performed by reduction of the corresponding (di)ketopiperazines[2,3] or by various cyclisation reactions, *e.g.* dialkylation of amines with bis(2-chloroethyl)amine[4] or intramolecular reductive coupling of diimines.[5] However, a more environmentally friendly and atom-economical[6] method for forming a carbon–nitrogen bond is the direct condensation between an amine and an alcohol, since this transformation only produces a molecule of water as the by-product.[7] Recently, several iridium[8] and ruthenium[9] catalysts were shown to mediate the alkylation of amines with alcohols. The mechanism involves dehydrogenation of the alcohol to the corresponding aldehyde/ketone followed by imine formation and reduction to the product amine with the liberated hydrogen from the first step (Scheme 1). We envisioned that the piperazine ring system could be formed in this way by cyclocondensation of a 1,2-diol with either a primary amine or a 1,2-diamine. Herein, we report our results on the synthesis of differently substituted piperazines in the presence of the trivalent iridium complex $[Cp^*IrCl_2]_2$.

The initial studies were performed with equimolar amounts of (±)-*trans*-1,2-diaminocyclohexane and ethylene glycol by reaction in a sealed flask overnight (Scheme 2). The commercially available



Scheme 1 Mechanism for amine alkylation with alcohols.

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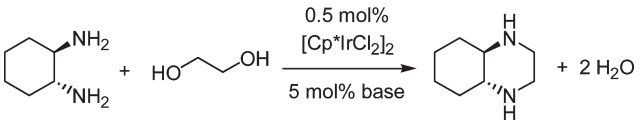
† Electronic supplementary information (ESI) available: General procedure, characterisation data and copies of ^1H and ^{13}C NMR spectra for all the prepared piperazines. See DOI: 10.1039/b712685a



Scheme 2 Iridium catalysed synthesis of a bicyclic piperazine.

complex $[Cp^*IrCl_2]_2$ was chosen since this catalyst has previously shown high reactivity in the coupling of primary amines with both primary and secondary alcohols.[10] First, we examined several different solvents with sodium bicarbonate as the base (Table 1, entries 1–5). Rewardingly, the desired reaction proceeded very well in toluene and water while dioxane gave a slightly lower yield. It is quite remarkable that water is a highly effective solvent for this transformation since the reaction goes through two imines. Apparently, the formation of these imines is not the rate limiting step in the overall transformation.

A number of experiments were then carried out in order to investigate the influence of the base. In the absence of a base, the reaction resulted in a lower yield due to incomplete conversion of the starting materials (entries 6 and 7). Lower yields were also observed when sodium carbonate or sodium acetate were employed while triethylamine gave a similar yield to sodium bicarbonate (entries 8–12). Experiments were also carried out with an acid as the additive. When the reaction in Scheme 2 was carried out in water in the presence of 10% of trifluoroacetic acid, the product piperazine was isolated in 98% yield. This is an interesting result and shows that the cyclocondensation can be promoted by both acids and bases. For general use, however, we selected the more convenient sodium bicarbonate as the additive with either toluene or water as the solvent.

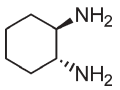
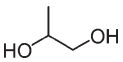
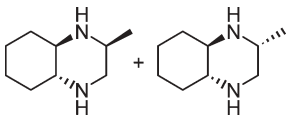
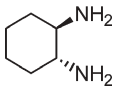
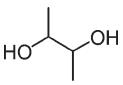
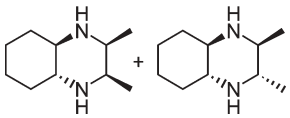
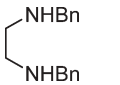
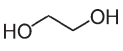
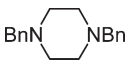
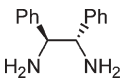
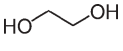
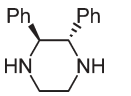
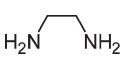
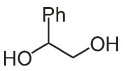
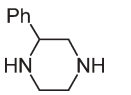
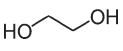
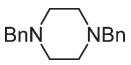
We then turned our attention to other substrates in order to explore the scope of the cyclocondensation reaction (Table 2). Propane-1,2-diol showed a similar reactivity to ethylene glycol in

Table 1 Solvent and base screening for the reaction in Scheme 2

Entry	Solvent	Base	Temp./°C	Yield[a] (%)
1	THF	$NaHCO_3$	67	5
2	Heptane	$NaHCO_3$	98	13
3	Dioxane	$NaHCO_3$	100	86
4	Toluene	$NaHCO_3$	110	94
5	Water	$NaHCO_3$	100	96
6	Toluene	None	110	78
7	Water	None	100	41
8	Toluene	Na_2CO_3	110	63
9	Water	Na_2CO_3	100	24
10	Toluene	NaOAc	110	53
11	Water	NaOAc	100	48
12	Toluene	Et_3N	110	94

[a] Isolated yield.

Table 2 Synthesis of substituted piperazines[a]

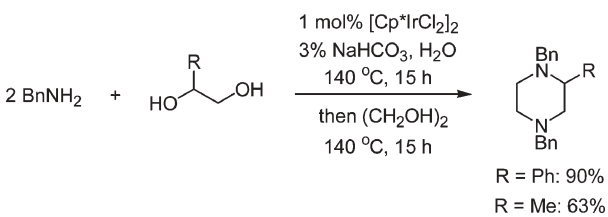
Entry	Amine	Diol	Product(s)	Solvent	Temp./°C	Yield[b] (%) (dr)[c]
1				Toluene	110	87 (3 : 1)
				Water	100	98 (>20 : 1)
2				Toluene	140	79 (1 : 1)
				Water	140	81 (3 : 1)
3				Toluene	140	74
				Water	140	73
4				Toluene	110	54[d]
				Water	100	60[d]/86[e]
5				Water	120	Quant.
6	$BnNH_2$			Neat	160[f]	94

[a] Reactions were performed overnight with equimolar amounts of amine and diol in the presence of 0.5 mol% $[Cp^*IrCl_2]_2$ and 5% of $NaHCO_3$. [b] Isolated yield. [c] Determined from ^1H NMR spectroscopy. [d] Reaction time 64 h. [e] 10% of trifluoroacetic acid was used instead of $NaHCO_3$. [f] Reaction time 6 h.

the reaction with *trans*-1,2-diaminocyclohexane and good yields were obtained in both toluene and water (entry 1). A new stereocentre is introduced in this reaction and the diastereoselectivity is highly dependent on the solvent. Butane-2,3-diol also reacted with an equimolar amount of 1,2-diaminocyclohexane, but in this case the reaction was slower and required a higher temperature in order to go to completion (entry 2). The reaction gave mainly two diastereomers which were identified as the *cis* and the *trans* product, with the former being the major product in water. Additional substituents were also allowed in the diamine and this was shown by the reaction between *N*,*N*′-dibenzyl-1,2-diaminoethane and ethylene glycol to give 1,4-dibenzylpiperazine (entry 3). The reactions in entries 2 and 3 required a temperature around 140 °C for full conversion which shows that secondary amines and secondary alcohols react significantly slower than the corresponding primary amines and alcohols. The addition of trifluoroacetic acid did not improve the reactions with the substituted substrates and in both entries 2 and 3 the cyclocondensation proceeded poorly with the acid as an additive. The reaction in water in entry 3 should be noted since the transformation with the secondary amine must go through an iminium ion/enamine and this does not seem to be severely hampered by the aqueous media. Optically pure (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane also participated in the cyclisation reaction with ethylene glycol, and the product showed no sign of racemisation according to the optical rotation (entry 4). This diamine reacted slower than 1,2-diaminocyclohexane and required almost 3 days for complete conversion. Notably, the reactivity and the yield could be improved in this case by using an acid as the additive. On the other hand, the simple diamine, 1,2-diaminoethane, reacted smoothly with (±)-1-phenylethane-1,2-diol to give 2-phenylpiperazine in quantitative yield (entry 5).

1,4-Dibenzylpiperazine in entry 3 is a symmetric molecule that could also be generated from benzylamine and ethylene glycol. This reaction was investigated in entry 6 and the initial experiments were performed in toluene or water at 140 °C. However, the reaction was slower than in entry 3 under these conditions and only gave about 45% yield. Therefore, it was attempted to leave out the solvent which required the reaction to be performed at 160 °C to ensure full conversion. Under these conditions, dibenzylpiperazine was obtained as a crystalline material and isolated in 94% yield after washing with water and filtration.‡

To further expand the scope of the reaction and to develop an alternative route to substituted piperazines we carried out a sequence where two different diols would participate in the cyclocondensation with a primary amine (Scheme 3). This was performed as a one-pot protocol where 1-phenylethane-1,2-diol or propane-1,2-diol was first allowed to react to completion with 2 equiv. of benzylamine to produce the corresponding 1,2-bis(benzylamino) compound. Since a secondary amine is converted much slower than a primary amine, the starting diol will



Scheme 3 Synthesis of 1,2,4-trisubstituted piperazines from two diols.

predominately react with benzylamine. Subsequently, ethylene glycol is added to the mixture and the reaction is heated again until full conversion into the piperazine is achieved. In this way, 1,4-dibenzyl-2-phenylpiperazine was formed in 90% yield from 1-phenylethane-1,2-diol while 1,4-dibenzyl-2-methylpiperazine was obtained in 63% yield from propane-1,2-diol. The lower yield in the latter case is due to a lower selectivity in the initial reaction between benzylamine and the diol. Both reactions were carried out in water at 140 °C which gave a higher yield than performing the reactions in neat conditions at 160 °C.

In summary, we have developed a new method for the synthesis of piperazines by using an iridium catalysed cyclocondensation of diols with either a primary amine or a 1,2-diamine. This constitutes a green and atom-economical transformation that can be performed in aqueous media and only produces water as a by-product.

We thank the Lundbeck Foundation for financial support. The Center for Sustainable and Green Chemistry is supported by the Danish National Research Foundation.

Notes and references

‡ **Synthesis of 1,4-dibenzylpiperazine (Table 2, entry 6)**: to a 5 mL screw-top vial were added $[Cp^*IrCl_2]_2$ (48 mg, 0.06 mmol), benzylamine (1.31 mL, 12.0 mmol), ethylene glycol (0.67 mL, 12.0 mmol) and $NaHCO_3$ (23 mg). The vial was flushed with argon, sealed and heated to 160 °C for 6 h. After cooling to room temperature, the flask was stored at 5 °C overnight. The solid reaction mixture was washed with water and filtered, and the filter cake was rinsed with a small amount of ether to give 1.50 g (94%) of the target compound as white crystals, mp 87–90 °C (lit.[11] mp 90–92 °C). δ_H (300 MHz, $CDCl_3$): 7.35–7.21 (m, 10H), 3.52 (s, 4H), 2.49 (bs, 8H); δ_C (75 MHz, $CDCl_3$): 138.2, 129.4, 128.3, 127.1, 63.2, 53.2.

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Appendix B

Nordstrøm, L. U.; Vogt, H.; Madsen, R. ’Amide synthesis from alcohols and amines by the extrusion of dihydrogen’, *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.

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Amide Synthesis from Alcohols and Amines by the Extrusion of Dihydrogen

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The amide bond is one of the most important linkages in organic chemistry and constitutes the key functional group in peptides, polymers, and many natural products and pharmaceuticals.[1] Amides are usually prepared by coupling of carboxylic acids and amines by the use of either a coupling reagent[2] or by prior conversion of the carboxylic acid into a derivative.[3] Alternative procedures include the Staudinger ligation,[4] aminocarbonylation of aryl halides,[5] and oxidative amidation of aldehydes.[6] However, all these methods require stoichiometric amounts of various reagents and lead to equimolar amounts of byproducts. In special cases, amides can be formed by catalytic procedures as shown for the Schmidt reaction between ketones and azides,[7] the Beckmann rearrangement,[8] and the amidation of thioacids with azides.[9]

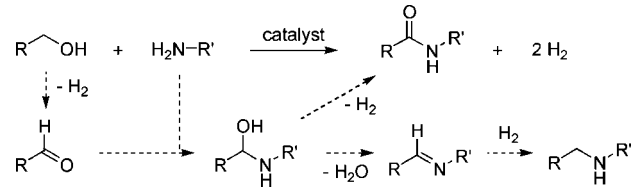
A more environmentally friendly protocol for amide synthesis is the direct amidation of amines with alcohols where two molecules of dihydrogen are liberated (Scheme 1). This unique transformation has only been described once before where a ruthenium pincer complex was used for the direct coupling of sterically unhindered primary amines and alcohols.[10] Presumably, the reaction proceeds through the intermediate aldehyde which reacts with the amine to give a hemiaminal that is subsequently dehydrogenated to the amide.[10] The last step of the mechanism is crucial since the hemiaminal may also eliminate water to generate an imine which can undergo hydrogenation with the liberated dihydrogen to form an amine. In fact, alkylation of amines with alcohols has been described with several ruthenium and iridium catalysts[11] and we have recently used this protocol for synthesis of piperazines from 1,2-diols and amines.[12]

In a study of new ruthenium catalysts for the alkylation of amines with alcohols we investigated various *N*-heterocyclic carbenes (NHC)[13] as ligands. Unexpectedly, we observed exclusive formation of amides in these reactions and none of the corresponding amines. Herein, we report the discovery of this new catalyst system for the direct synthesis of amides from alcohols and amines.

The first experiment was carried out with 2-phenylethanol, benzylamine, and 5% of the catalyst in refluxing toluene. The catalyst was generated *in situ* from $Ru(PPh_3)_3Cl_2$, imidazolium salt **A**, and potassium *tert*-butoxide where the latter deprotonates **A** to generate the corresponding carbene[13] (Figure 1).

The reaction afforded *N*-benzyl 2-phenylacetamide in 15% isolated yield after 16 h with a significant amount of alcohol and amine still remaining (Table 1, entry 1). None of the amide was formed in the absence of the carbene and the yield did not improve by changing the solvent, the temperature, or the ratio between the ruthenium complex and the carbene. The ruthenium precatalyst was therefore replaced with $Ru(COD)Cl_2$ in order to investigate the influence of the phosphine ligand. In the absence of phosphines no amide was observed (entry 2). Monodentate phosphine ligands with a larger cone angle than triphenylphosphine afforded a slightly better yield of the amide (entries 3−6) while bidentate phosphine ligands resulted in no reaction.[14] The carbene precursors were then changed

Scheme 1. Amide Formation from Alcohols and Amines



and this proved to have a more decisive impact on the amidation (entries 8−14). Unsaturated carbenes with aliphatic *N*-substituents gave significantly better yields with **D** as the best result while the corresponding saturated carbenes derived from **F**−**H** all gave lower yields. The phosphine ligand was investigated again and it was found that tricyclopentylphosphine ($PCyp_3$) gave a minor improvement (entries 15−19). For general use it was decided to utilize the more stable and crystalline HBF_4 salt (entry 19) which gave the same isolated yield of the amide as the free phosphine.

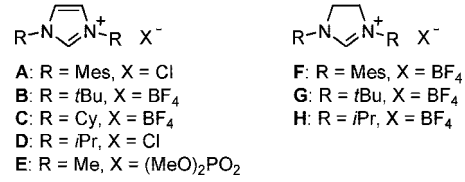
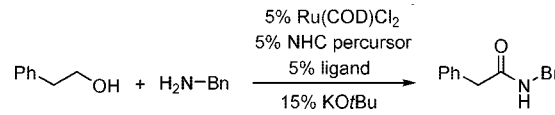


Figure 1. NHC precursors.

Table 1. Amidation with Different NHC and Phosphine Ligands[a]

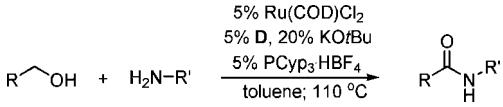


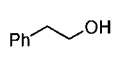
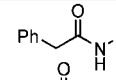
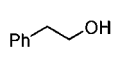
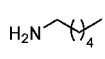
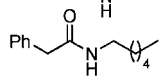
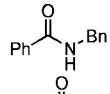
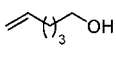
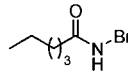
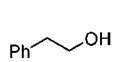
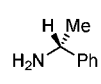
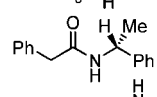
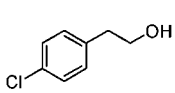
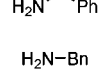
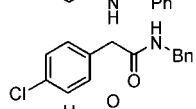
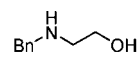
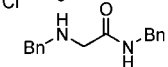
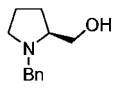
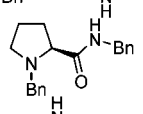
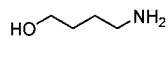
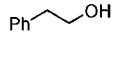
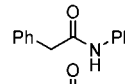
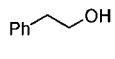
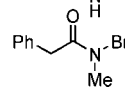
entry	NHC precursor	ligand	yield[b]
1	**A**		15%[c]
2	**A**	none	0%
3	**A**	PPh_3	21%
4	**A**	P(*o*-tol)$_3$	26%
5	**A**	PCy_3	27%
6	**A**	P*t*Bu$_3$	22%
7	**A**	P*n*Bu$_3$	9%
8	**B**	PCy_3	68%
9	**C**	PCy_3	84%
10	**D**	PCy_3	92%
11	**E**	PCy_3	53%
12	**F**	PCy_3	45%
13	**G**	PCy_3	22%
14	**H**	PCy_3	48%
15	**D**	PCy_2Ph	54%
16	**D**	PCy_2(*o*-biphenyl)	90%
17	**D**	P*t*Bu$_2$(*o*-biphenyl)	34%
18	**D**	$PCyp_3$	98%
19	**D**	$PCyp_3 \cdot HBF_4$	92%[d]

[a] In toluene at 110 °C; 24 h. [b] GC-yield. [c] Isolated yield from reaction with 5% of $Ru(PPh_3)_3Cl_2$. [d] Run using 20% of KO*t*Bu.

10.1021/ja808129p CCC: $40.75

Table 2. Amidation of Amines with Alcohols



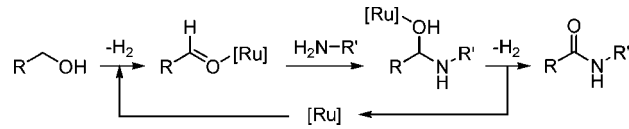
Entry	Alcohol	Amine	Amide	Yield[a]
1				93%[b]
2				100%[b]
3				78%
4				60%
5				70%
6				83%[b]
7				90%
8				60%
9				65%
10				21%[c]
11				40%[c]

[a] Isolated yield. [b] Ru(COD)Cl_2 (2%), ligands (2%), and base (8%). [c] In mesitylene at 163 °C.

With these optimized conditions in place the scope and limitation of the method could now be explored. A range of different primary alcohols were reacted with primary amines to afford the corresponding secondary amides in 60−100% isolated yield (Table 2, entries 1−9).

Sterically unhindered alcohols and amines gave the amide in high yield (entry 1 and 2). Benzyl alcohol was converted into benzamide (entry 3) while hex-5-en-1-ol gave the hexanamide with concomitant reduction of the olefin (entry 4). An optically pure amine could be employed and the product showed no sign of racemization according to optical rotation (entry 5). An aryl chloride also participated in the amidation (entry 6) while essentially no reaction occurred with the corresponding aryl bromide (data not shown). *N*-Benzylethanolamine could be coupled with benzylamine in high yield (entry 7) which shows that the transformation is selective for a primary amine. Optically pure *N*-benzyl-L-prolinol was converted into *N*,*N*′-dibenzyl-L-prolinamide with no sign of epimerization (entry 8). The amidation could also be carried out in an intramolecular fashion as illustrated with the formation of γ-butyrolactam (entry 9). Aniline and secondary amines, on the other hand, did not react with primary alcohols at 110 °C. However, when the temperature was raised to 163 °C complete conversion of the alcohol was observed. At this temperature, aniline and *N*-methylbenzylamine gave the amide in low to moderate yield while the remaining portion of the alcohol underwent self-condensation into the corresponding ester (entry 10 and 11).

Scheme 2. Mechanism for Ruthenium-Catalyzed Amide Formation



The amidation presumably follows the mechanism in Scheme 2 and does not proceed through an intermediate ester. The latter was confirmed by treating 2-phenylethyl 2-phenylacetate with benzylamine and the catalyst, which afforded none of the amide in Table 2, entry 1. The reaction between benzaldehyde and benzylamine under the same conditions led to exclusive formation of the corresponding imine and neither amide nor amine was observed. The imine does not react in the presence of the catalyst and this did not change by adding water or by conducting the reaction under a dihydrogen atmosphere. Imine formation has never been detected by GC in any of the experiments in Table 2. This indicates that the reaction proceeds through an aldehyde, but that the aldehyde stays coordinated to the metal (Scheme 2). Subsequent attack by the amine affords the hemiaminal which also stays coordinated to the metal. The amide is then formed after β-hydride elimination and at no time is a free aldehyde or hemiaminal released from the catalyst since this would lead to the formation of an unreactive imine.

In conclusion, we have developed a novel method for the amidation of amines with alcohols. The reaction is performed with a simple catalyst prepared from a ruthenium precursor, an *N*-heterocyclic carbene and a phosphine ligand. This system presents new opportunities for the preparation of a key functional group in organic chemistry.

Acknowledgment. We thank the Danish National Research Foundation for financial support.

Supporting Information Available: General experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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